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TRANSMITTAL OF UTILITY APPLICATION UNDER 37 C.F.R. §1.53		
	Attorney Docket No.	18021-2901 (Box Seq)
	First named inventor	Paul Sternberg
	Express mail label #	EL516975777US
	Date of mailing	January 6, 2000

Application Elements

1. [X] Fee Transmittal Form
2. [X] Specification containing 71 pages (including claims and Abstract) and a Sequence Listing (62 pages).
   a. Title: POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON
   b. Number of claims: 88
3. [X] 5 sheets of drawings with 4 Figs.
4. [ ] Copy of Declaration from parent application
5. [X] Sequence Listing (62 pages)
   [X] Paper copy (identical to computer copy)
   [X] Computer readable copy
   [ ] Verified statement

Accompanying Application Papers

6. [ ] Copy of assignment from prior
7. [X] Copy of Small Entity Statements filed in priority application
8. [ ] Preliminary Amendment
9. [X] Return Receipt Postcard

SIGNATURE OF ATTORNEY/AGENT

HELLER EHRMAN WHITE & McAULIFFE

Stephanie Seidman
Registration Number: 33,779

[X] Benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Application Serial No. 60/115,127, filed January 6, 19990 is claimed.

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FEE TRANSMITTAL ACCOMPANYING UTILITY APPLICATION UNDER 37 C.F.R. §1.53	Attorney Docket No.	18021-2901
	First named inventor	Paul Sternberg
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FEE CALCULATION FOR CLAIMS AS AMENDED

a)	Basic Fee	$ 690.00
b)	Independent Claims 15 - 3 = 12 x $ 78.00	$ 936.00
c)	Total Claims 88 - 20 = 68 x $ 18.00	$ 1224.00
d)	Fee for Multiple Dependent Claims - $230.00	$ 0.00
	TOTAL FILING FEE	$ 2850.00

[X] Statement(s) of Status as Small Entity reducing Fee by one-half to $1425.00

[X] A check in the amount of $1425.00 to cover the fee for filing the application.

[X] The Commissioner is hereby authorized to charge any fees that may be required in this application during its entire pendency, or credit any overpayment, to Deposit Account No. 08-1641. If proper payment is not enclosed, such as a check in the wrong amount, unsigned, post-dated, otherwise improper or informal, or absent, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 08-1641 during the entire pendency of this application. This sheet is filed in duplicate.

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ATTORNEY DOCKET NO. 06618/391001/CIT2919

Applicant or Patentee: Paul W. Sternberg et al.
Serial or Patent No.:
Filed or Issued: 1/6/99
For: CAENORHABDITIS ELEGANS STRAINS PERTURBED IN POLYCYSTIN FUNCTION

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(d)) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization: California Institute of Technology
Address of Organization: 1200 East California Blvd.
Type of Organization:

[X] UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
[ ] TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3))
[ ] NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
(NAME OF STATE:)
(CITATION OF STATUTE:)
[ ] WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA
[ ] WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
(NAME OF STATE:)
(CITATION OF STATUTE:)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled CAENORHABDITIS ELEGANS STRAINS PERTURBED IN POLYCYSTIN FUNCTION by inventor(s) PAUL W. STERNBERG AND MAUREEN M. BARR described in

[X] the specification filed herewith.
[ ] application serial no. , filed .
[ ] patent no. , issued .

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

Full Name: ______

Address: ______

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [X] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status when any new rule 53 application is filed or prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Name: Adam Cochran

Title: The Intellectual Property Counsel

Address: 1200 East California Blvd., Pasadena, CA 91125

Signature: [signature] Date: January 6, 1999

POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON

RELATED APPLICATIONS

For U.S. purposes, benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Application Serial No. 60/115,127, entitled "*CAENORHABDITIS ELEGANS* STRAINS PERTURBED IN POLYCYSTIN FUNCTION" to Paul W. Sternberg and Maureen M. Barr, filed January 6, 1999, is claimed herein. The subject matter of U.S. Provisional Application Serial No. 60/115,127 is incorporated in its entirety by reference.

FIELD OF INVENTION

Systems and assays for identification of compounds that can be used to treat polycystic kidney disease (PKD) are provided. Nematode orthologs of genes involved in PKD are identified and associated with mating behaviors. In particular, nematodes, such as *Caenorhabditis elegans*, that express mutant and wild-type orthologs of human genes involved in this disease, are used to study the functions of the proteins encoded by the genes, to screen for other genes involved in the disease, to identify mutations involved in the disease, and to screen for drugs that affect PKD. Hence an animal model is provided that permits study of the etiology of polycystic kidney disease and provides a tool to identify the genes and factors involved in the disease pathway, and to identify compounds that may be used to treat or alter the disease progression, lessen its severity or ameliorate symptoms.

BACKGROUND

Polycystic Kidney Diseases

Polycystic kidney diseases (PKD) are a group of disorders characterized by the presence of a large number of fluid-filled cysts throughout grossly enlarged kidneys (Gabow *et al.* (1992) *Diseases of the Kidney*, Schrier *et al.*. eds.). In humans, PKDs can be inherited in autosomal dominant (ADPKD) or autosomal recessive (ARPKD) forms.

ADPKD is the more common form and is the most common, dominantly-inherited kidney disease in humans, occurring at a frequency of about 1 in 800. ARPKD occurs at a frequency of about 1 in 10,000.

ADPKD is the most common single-gene disorder leading to kidney failure (see, Emmons *et al.* (1999) *Nature 401*:339-340). Since ADPKD is inherited as an autosomal dominant disorder, children of affected parents have a one in two chance of inheriting the disease. Although the kidney is the most severely affected organ, the disease is systemic and affects the liver, pancreas cardiovascular system and cerebro-vascular system. The major manifestation of the disorder is the progressive cystic dilation of renal tubules (Gabow (1990) *Am. J. Kidney Dis. 16*:403-413), leading to renal failure in half of affected individuals by age 50. Microdissection, histochemical and immunologic studies show that cysts in ARPKD kidneys arise from focal dilations of medullary collecting ducts (McDonald (1991) *Semin. Nephrol. 11*:632-642). Although end-stage renal failure usually supervenes in middle age (ADPKD is sometimes called adult polycystic kidney disease), children may occasionally have severe renal cystic disease.

ADPKD-associated renal cysts may enlarge to contain several liters of fluid and the kidneys usually enlarge progressively causing pain. Other abnormalities such as hematuria, renal and urinary infection, renal tumors, salt and water imbalance and hypertension frequently result from the renal defect. Cystic abnormalities in other organs, including the liver, pancreas, spleen and ovaries are commonly found in ADPKD. Massive liver enlargement can causes portal hypertension and hepatic failure. Cardiac valve abnormalities and an increased frequency of subarachnoid and other intracranial hemorrhage have also been observed in ADPKD. Progressive renal failure causes death in many ADPKD patients and dialysis and transplantation are frequently required to maintain life in these patients.

Numerous biochemical abnormalities associated with this disease also are observed. These include defects in protein sorting, the distribution of cell membrane markers within renal epithelial cells, extracellular matrix, ion transport, epithelial cell turnover, and epithelial cell proliferation.

Three distinct loci have been shown to cause phenotypically indistinct forms of the AKPKD in humans. These include polycystin-1 (PKD1) on chromosome 16, polycystin-2 (PKD2) on chromosome 4, and polycystin-3 (PKD3) (see, *e.g.*, Reeders *et al.* (1985) *Nature 317*:542-544; Kimberling *et al.*. (1993) *Genomics 18*:467-472; Daoust *et al.* (1995) Genomics, 25:733-736). The ARPKD mutation is on human chromosome 6 (Zerres *et al.* (1993) *Nature Genet. 7*:429-432). Two proteins polycystin-1 (PKD1) and polycystin-2 (PKD2) are defective in human autosomal dominant polycystic kidney disease.

Mutations in either PKD1 or PKD2 cause almost indistinguishable clinical symptoms. Mutations in PKD1 or PKD2 account for 95% of autosomal dominant polycystic disease (Torres *et al.* (1998) Current Opinion in Nephrology and *Hypertension 7*:159-169) with greater than 85-90% of disease incidence being due to mutations in PKD1.

The human PKD1 protein is an approximately 4,300 amino-acid integral-membrane glycoprotein with a large amino-terminal extracellular domain and a small, carboxy-terminal cytoplasmic tail. The human PKD1 gene (see, *e.g.*, U.S. Patent No. 5,891,628), including the complete nucleotide sequence of the gene's coding region (se SEQ ID No. 1) and encoded amino acid sequence, is known (see, SEQ ID No. 2). The predicted structure of the domains suggested that it is involved in cell-cell interactions or in interactions with the extracellular matrix. The PKD2 protein has similarities to PKD1, but its topology and domain structure suggest that it might act as a subunit of a cation channel. These proteins have been shown to interact directly (Mochizuki *et al.* (1996) *Science 272*:1339-1342, Qian (1997) *Nature Genetics 16*:179-183).

Although these genes have been implicated in the disorders their role in it etiology is not established. In addition, while studies of kidneys from ADPKD patients exhibit a number of different biochemical, structural and physiological abnormalities, the disorder's underlying causative biochemical defect is not known. Hence the molecular mechanisms leading to cyst enlargement and progressive loss of renal function in the PKDs are not understood. Presently there are no cures or effective treatments, other than palliative treatments, for these diseases. Hence there is a need to understand the underlying biochemistry and physiology of the ADPKD and to provide treatments.

Therefore, it is an object herein to provide a means to identify the underlying biochemistry and genetics of these diseases and to provide a means to identify compounds for use in treatment of these diseases.

SUMMARY

Isolated genes, cDNA and encoded proteins from nematodes that participate in a pathway leading to an observable phenotype are provided. In particular, it is shown herein, that a mutation in *C. elegans*, which gives rise to males that are defective in certain aspects of mating behavior, lies in a gene designed herein *lov-1* (location of vulva), and that this gene is an ortholog of the mammalian, particularly human, PKD1 gene. A mutation in a gene designated *pkd-2* herein also gives rise to these behaviors. This gene is shown to be an ortholog of the mammalian, including human, PKD2 gene.

The expression pattern of *lov-1* and *pkd-2* was studied and it was found that promoter sequences of both genes cause reporter genes to be expressed in the rays and the hook sensory neurons required for 'response" and vulva location. Thus showing that the LOV-1 and PKD-2 proteins are involved in chemosensory or mechanosensory signal transduction in sensory neurons.

Hence genes that are components of a pathway in nematodes are provided and are shown to be linked to observable behaviors. Each of the encoded proteins, LOV-1 and PKD-2 are components in a pathway, which appears to be a signal transduction pathway, that leads to the observed phenotype. The genes from the nematode *Caenorhabditis elegans* are exemplified herein.

The pathway is shown to be homologous to the pathway in which the human polycystins, PKD1 and PKD2, participate. In particular, it is shown herein, that a mutation in nematodes, which gives rise to males that are defective in mating behavior, lies in a gene designated herein *lov-1* (location of vulva). This gene, *lov-1*, is shown herein to be required for two male sensory behaviors, 'response' and 'location of vulva' (Lov).

A second gene, designated *pkd-2*, that affects this behavior in a similar manner is also identified and provided herein. The encoded proteins are also provided. The gene, cDNA, and encoded protein is also provided. In an exemplary embodiment, the *C. elegans* genome sequence was used to isolate *pkd-2*. This gene is a nematode ortholog of the mammalian, particularly human PKD2 gene. Strains that contain knock-out mutants of this gene also exhibit the defective mating behaviors.

In an exemplary embodiment, provided herein are the *C. elegans* genes, designated *lov-1* and *pkd-2*. SEQ ID No. 3 sets forth the complement (*i.e.*, the non-coding strand) of the *lov-1* gene from *C. elegans*. SEQ ID No. 4 sets forth the sequence of amino acids of the protein (N-terminus to C-terminus)). SEQ ID No. 5 sets forth the complement (*i.e.*, the non-coding strand) of the *C. elegans pkd-2* gene from *C. elegans*. SEQ ID No. 6 sets forth the encoded sequence of amino acids.

Also provided are the mutants of the genes, *lov-1*, and *pkd-2* and the resulting mutant encoded proteins. Nucleic acid molecules encoding mutants of these genes are also provided. For example, deletion mutants of these genes, particularly deletion mutants that substantially or

completely knock-out gene product function, are provided. Thus, nucleic acid molecules containing deletions of each of these genes and deletion mutants that alter the phenotype of nematodes, such as *C. elegans*, that contain these mutant genes are also provided. Constructs, vectors, plasmids and strains containing each of the nucleic molecules are also provided. Also provided are strains defective in these genes.

Also provided are strains containing the mutant nucleic acids. Strains that manifest the defective male sensory behaviors are also provided herein. Constructs containing the genes, vectors containing the constructs, cells containing the vectors and transgenic *C. elegans*. Assays that use these strains of *C. elegans* are also provided.

As noted, it is shown herein that these genes are human homologs of the human genes that encode polycystins, proteins polycystin-1 (PKD1) and polycystin-2 (PKD2), which are defective in human autosomal dominant polycystic kidney disease. Hence, the genes and nematode strains provide model systems for studying this pathway, identifying additional components of the pathway, and for use in drug screening assays to identify compounds affect the pathway and/or compounds that serve as leads for development of drugs for treatment of polycystic kidney disease.

Each gene is shown to affect two sensory behaviors in *C. elegans*. One behavior designated "Response" and refers to the response of males to hermaphrodites; and the other behavior, designated "Lov" refers to location of the vulva by the male. Strains that are defective in either or both of these genes are also provided. In particular deletion mutants are provided.

By correlating the phenotypic behaviors with wild-type or defects in these genes, nematodes, such as *C. elegans*, can be used to identify other genes involved in this pathway and also means for direct screening for lead candidate compounds for drugs for treatment of PKD. Identification of additional genes necessary for PKD function can provide additional

diagnostic tools for PKD. Hence, provided herein are mutant strains of *C. elegans* and assays that use the strains.

Also provided herein are assays that employ the constructs, vectors, plasmids and strains containing each of the nucleic molecules are also provided. In particular, in one type of assays wild-type nematodes are mutagenized or treated with a test compound, and those that exhibit a change in behavior are identified.

In other types of assays, nematodes that are defective in LOV and/or Response are mutagenized or treated with a compound, and those that exhibit a change in behavior are identified. Test compounds or mutations responsible for the change in behavior are identified. Such compounds are candidates for treatment of PKDs.

Among these methods are those that involved contacting a nematode that exhibits normal mating behavior with a test compound; and selecting compounds that result in altered mating behavior, wherein the altered mating behavior comprises alteration in the behavior involving location of vulva and/or response to contact with the hermaphrodite.

Also provided are methods for identifying genes involved in autosomal dominant polycystic kidney disease (ADPKD). Among these methods are those in involving mutagenizing nematodes that exhibit normal mating behavior; and identifying and selecting nematodes that exhibit altered mating behavior, where the altered mating behavior is manifested as an alteration in location of vulva and/or response to contact with the hermaphrodite. The mutated gene(s) responsible for the alteration in behavior are then identified. Databases or libraries of mammalian genes can be screened to identify homologs of these genes, which can then serve as therapeutic or diagnostic targets or aid in elucidation of the disease pathology.

Methods for identifying compounds that are candidate therapeutic agents for treatment of autosomal dominant polycystic kidney disease (ADPKD) are provided. Among the methods are those in which normal

males are treated with a candidate compound. Compounds that result in changes in mating behaviors or changes in mating efficiencies are selected.

Methods for identifying genes involved in the disease pathway are also provided. Among the methods are those in which normal males are mutagenized. Offspring that exhibit changes in mating behaviors or changes in mating efficiencies are selected and mutated genes are identified and shown to be part of the pathway. Mammalian, particularly human, homologs of the mutated genes are then identified. Such genes are likely to be part of the disease pathway. Such genes can serve as therapeutic targets and disease markers for diagnostic.

Other assays use nematode strains that have mutations in either or both of *lov-1* or *pkd-2*. As described herein, suppressor and enhancer genetics can be used to assign functions to genes, to assign genes to pathways, to identify the key switches in these pathways and to provide a sensitive assay to identify new genes in a pathway and lead compounds that modulate the activity of genes and/or gene products in the pathway.

Assays that identify the role of PKD proteins in sensory function are also provided. Since *lov-1* and *pkd-2* are expressed in CEM neurons, they have activity in other sensory functions, such as finding the mating partner at a distance. Accordingly assays using sexual chemotaxis or kinesis are provided. For example, males that are mutagenized or treated with a test compound are placed on a surface containing males and hermaphrodites, and are then observed to assess whether they can choose between males and hermaphrodites. If the male is defective in this sensory function, it will not distinguish between males and hermaphrodites.

Assays that use dominant negative forms of PKD in nematodes or in other cells to identify mutations and/or compounds that inhibit PKD function are also provided. Transgenic nematodes that express a version of the LOV-1 or PKD-2 protein that inhibits the activity of LOV-1 and/or

PKD-2 as assessed by manifestation of the altered LOV and/or response phenotypic behavior(s) are used in these assays. Transgenic nematodes can be produced by any method known to those of skill in the art, including, but are limited to, injection of the nucleic acid into the embryos or cells of the animal. Transgenic nematodes that contain a dominant negative lov-1 or pkd-2 transgene are contacted with a test compound, and compounds that interfere with a remaining activity of the *LOV-1* or *PKD-2* protein are selected. Alternatively, these transgenic nematodes are mutagenized and mutants that lose a remaining activity are selected and the gene or mutation responsible for the loss or that contributes to the loss is identified.

Assays based on localization and trafficking of LOV-1 and/or PKD-2 within a cell or cells are also provided. These assays can identify regulators and factors necessary for synthesis and transport of *LOV-1* and/or *PKD-2* proteins and employ strains in which LOV-1 and PKD-2 are expressed linked to a detectable label, such as a fluorescent protein. These strains are used to assess the effects of compounds or mutagenesis on the trafficking patterns of *LOV-1* and *PKD-2* and cellular location(s) of the proteins in the animal. Identified mutations can be mapped and the genes identified. If mammalian, particularly human, homologs of these identified genes exist, such genes can serve as therapeutic or diagnostic targets and can aid in elucidation of the disease in mammals, particularly humans.

Assays for identification of transcriptional regulators of expression of *lov-1* and/or *pkd-2* are also provided. These assays screen for loss or alteration of expression of either gene and use transgenic nematodes with a reporter gene, such as a gene encoding a FP or lacZ or other detectable product, linked to the nucleic acid encoding *lov-1* or *pkd-2*. The animal is mutagenized or treated with a test compound and loss of expression or reduction in expression of either gene is assessed. These assays identify regulators of and factors that affect *lov-1* and *pkd-2* expression.

Mammalian, particularly human homologs of these regulators and factors are identified. Such regulators and factors can be therapeutic or diagnostic targets, and/or can aid in developing an understanding of the development and progression of PKD in mammals.

Kits for performing the assays, particularly, the drug screening assays, are also provided. The kits include transgenic or wild-type nematodes or both that express either wild-type or a mutant or a transgenic form of *lov-1* and/or *pkd-2*. The nematodes may be on plates, in wells or in any form suitable for the assays. Kits containing nucleic acid encoding either of the two genes or probes based upon these sequences or reporter gene constructions containing all or portions of either or both genes are also provided. The nucleic acids may be in solution, in lyophilized or other concentrated form, or may be bound to a suitable substrate. The kits can include additional reagents for performing the assays, such reagents include any for performing any of the steps of the methods. The kits include instructions for performing the assays.

DESCRIPTION OF FIGURES

Figure 1 depicts male mating behavior of *C. elegans.* The hermaphrodite is larger than the male and her vulva is depicted as a slit on the ventral, posterior third of her body. The male tail is place flush on the hermaphrodite, ventral side down. His spicules are depicted by a line in the tail. The hook is anterior to the spicules, the post cloacal sensilla is posterior. Sequence 1 illustrates wild-type male Lov. Sequence 2 represents hook ablated aberrant Lov behavior (passing and slow search). Sequence 3 portrays *lov-1(sy552)* mutant behavior (passing and eventually stopping).

Figure 2 depicts the molecular nature of *lov-1.* **a**, Genetic and physical maps of the *lov-1* region on chromosome 2. Genetic markers are shown. Boundaries of a *lov-1* deletion *(mnDf21)* and non-deletion *(eDf21)* are indicated. + designate rescue of *lov-1(sy552)* mutant males. Numbers in parentheses indicate the ratio of rescuing stable lines to total

stable lines examined. **b**, *lov-1* gene structure. Exons are boxed. Genefinder predicts two ORFs, ZK945.10 (9 exons) and ZK945.9 (19 exons). RT-PCR reveals *lov-1* corresponds to the combination of ZK945.10 and ZK945.9. The arrow indicates the 1059 bp deletion in *lov-1 (sy582Δ)* **c**, lov-1::GFP (green fluorescent protein) expression constructs, patterns, and phenotypes in wild-type background. **d**, *lov-1* encodes a membrane associated protein with homology to the polycystin and voltage-activated channel families. A schematic representation of LOV-1 is shown to demonstrate domains of the protein. These include the amino terminus that is serine/threonine rich with multiple potential glycosylation sites, an ATP/GTP binding domain (indicated by the asterisks), followed by two polycystin blocks of homology. Block 1 is exclusively homologous to PKD1, while Block 2 shows homology with all polycystins and also the family of voltage activated CA^{2+}channels. Block 1 is a conserved domain of unknown function, that also occurs at the N-terminus of most 5-lipoxygenases. Identity (%) and number of identical amino acids (in parentheses) between LOV-1 and a particular polycystin is indicated. Although LOV-1 lacks the carboxy terminal coiled-coil domain of all known polycystins, a coiled-coil is predicted in the middle of LOV-1 using the most stringent criteria for the COILS program (data not shown). Y73F8A.B+A was identified in a Blast search of unpublished sequences available through the Sanger Center and is more similar to PKD2 (30% identity, 48% similarity, 13% gaps over 752 aa) than LOV-1 (25% identity, 44% similarity, 14% gaps over 367 aa).

Figure 3 shows the *lov-1* and *pkd-2* genomic structures, constructs, rescue date and expression patterns; the line above *lov-1* indicates the 1,059 bp deletion in *lov-1(sy582Δ)*; numbers in parentheses indicate the ratio of rescuing stable lines to the number of stable lines examined, DN is dominant negative.

Figure 4 shows that *lov-1::GFP1* and PKD-2::GFP2 are colocalized to cell bodies and dendrites and are specifically expressed in adult male sensory neurons; the spicules, hook structure and posteriomost fan region autofluoresce; Arrows indicate neuronal cell bodies and arrowheads denote dendrites or ciliated endings. **a-c** *lov-1::GFP1*: (a) HOB and ray cell bodies (arrows), HOGB dendridic process (arrowhead); (b) HOB and ray process 5 (arrowheads); (c) Ciliated endings in nose tip from male specific cephalic CEM neurons (cell bodies not shown). **d-f** *pkd-2::GFP2*: (d) ray cell bodies (arrow) and ray process 2 (arrowhead); (e) ray process 5 (arrowhead); (f) male-specific celphalic CEM ciliated endings (arrow) Scale bar corresponds to 20 μm.

DETAILED DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. *Caenorhabditis elegans* nomenclature is well understood by those of skill in this area (see, *e.g.*, *Methods in Cell Biology C. elegans* I, and II, Cold Spring Harbor Press Books, Shakes, Epstein eds).

All patents, patent applications and publications referred anywhere herein, including the background, are, unless noted otherwise, incorporated by reference in their entirety. In the event a definition in this section is not consistent with definitions elsewhere, the definition set forth in this section will control.

As used herein, nematode is intended to refer generally to the class Nematoda or Nematoidea and includes those animals of a slender cylindrical or thread-like form commonly called roundworms. Among those species, members of the genus *Caenorhabditis* are preferred, but species that can be cultured in the laboratory may be used.

As used herein, the term "mutant," as in "nematode mutant" or "mutant nematode," is intended to refer generally to a nematode which

contains an altered genotype, preferably stably altered. The altered genotype results from a mutation not generally found in the genome of the wild-type nematode.

As used herein, a mutant gene, such as a mutant *lov-1* or *pkd-2* gene, refers to a gene that is altered, whereby a nematode with such gene, expresses an altered phenotype compared to a nematode with the wild type gene, such as a the genes set forth in SEQ ID Nos. 3 and 5 (which set forth the non-coding strands). Mutations include point mutations, insertions, deletions, rearrangements and any other change in the gene that results in an altered phenotype. Deletion mutants that eliminate the function of the encoded protein (knock-out mutations) are exemplified herein. Not all mutantations necessarily completely destroy the activity of the protein.

As used herein, "normal mating behavior" means that the animal exhibits behavior typical of wild-type nematodes with respect to the location of vulva (Lov) and response to of males to hermaphrodites. Thus a male that exhibits "normal mating behavior" upon encountering a hermaphrodite, ceases forward motion, places his tail flush on the hermaphrodite, commences backing along her body, and turns at her ends until he encounters her vulva and stops. This is the behavior of a *lov-1(+)* male. Mutant males defective in *lov-1* frequently do not respond to contact with the hermaphrodite and continue blindly moving forward. When response is initiated, *lov-1* mutants back and turn normally but pass the vulva at a high frequency. Thus, they can mate with paralyzed or otherwise slow moving hermaphrodites.

As used herein, a mammalian homolog of a nematode gene refers to a gene that encodes a protein that exhibits identifiable sequence homology and conservation of structure. The degree of sequence homology between a mammalian and nematode protein or gene to be considered hmologs, depends upon the gene considered but is typically at least about 30% at the protein level. An ortholog will typically have

greater sequence similarity, and conservation of structure and often function. Methods and criteria for identifying mammalian, including human, homologs of nematode genes are known to those of skill in the art and involve a comparison of the sequence and structural features of the encoded protein.

As used herein, a dominant negative mutation is a mutation that encodes a polypeptide that when expressed disrupts that activity of the protein encoded by the wild-type gene (see, Herskowitz (1987) *Nature* *329*:219-222). The function of the wild-type gene is blocked, a cloned gene is altered so that it encodes a mutant product that inhibits the wild-type gene product in a cell or organism. As a result, the cell or organism is deficient in the product. The mutation is "dominant" because its phenotype is manifested in the presence of the wild-type gene, and it is "negative" in the sense that it inactivates the wild-type gene function. It is possible to do this because proteins have multiple functional sites.

As used herein, a "library" of nematodes is a collection of a plurality of nematodes, typically more than 10, preferably more than 100. Typically a library will include variety of different nematodes and may include wild-type and mutant nematodes and a sufficient number to achieve the intended purpose for which the library is used..

As used herein, a gene encoding *LOV-1* protein refers to a gene (a sequence of nucleotides including introns, and exons, and optionally transcriptional regulatory sequences) from any nematode that encodes a protein that performs the same function in the nematode as the LOV-1 protein provided herein. Such protein can be identified using the methods provided herein for identifying it in *C. elegans*, or by isolating cDNA encoding the protein using probes constructed from the nucleic acid provided herein to isolate it using standard methods. Typically the coding sequence of the gene provided herein will hybridize along its length to the coding sequence of a related gene under conditions of at least low stringency, preferably moderate stringency, and likely under

conditions of high stringency. Nucleic acid encoding a LOV-1 protein includes any nucleic acid molecule, DNA, cDNA, RNA, that encodes a protein that has substantially the sequence of amino acids set forth in SEQ ID No. 4 and encodes a protein that has the same activity as this protein. Minor sequence variations from species to species and even among a species are considered to be substantially the same sequence. Such nucleic acid will hybridize to the nucleic acid encoding the proteins provided herein under conditions of at least low stringency, preferably moderate stringency and more preferably high stringency.

As used herein, a gene encoding *PKD-2* protein from a nematode is similarly defined, except that it has the substantially the same sequence as the sequence of amino acids set forth in SEQ ID No. 6. Having identified these proteins and functions therefor in *C. elegans* permits similar identification in other nematode species.

As used herein, stringency conditions refer to the washing conditions for removing the non-specific probes and conditions that are equivalent to either high, medium, or low stringency as described below:

1) high stringency: 0.1 x SSPE, 0.1% SDS, 65°C
2) medium stringency: 0.2 x SSPE, 0.1% SDS, 50°C
3) low stringency: 1.0 x SSPE, 0.1% SDS, 50°C.

It is understood that equivalent stringencies may be achieved using alternative buffers, salts and temperatures.

As used herein, percentage or amount or degree of sequence identity is used interchangeable with homology and refers to sequence identity or homology determined using standard alignment programs with gap penalties and other parameters set to the manufacturer's default settings. It is understood that for relatively high levels of sequence identity or homology, the particular program selected and/or defaults set for various parameters, do not substantially affect the results. Hence, for example, a requirement for 90% sequence identity of a nucleic acid sequence with another can be determined using any program known to

the skilled artisan or manually, and that such percentage can encompass about 85% to 95% identity.

As used herein, reference to a drug refers to a chemical entity, whether in the solid, liquid, or gaseous phase that is capable of providing a desired therapeutic effect when administered to a subject. The term "drug" should be read to include synthetic compounds, natural products and macromolecular entities such as polypeptides, polynucleotides, or lipids and also small molecules, including, but are not limited to, neurotransmitters, ligands, hormones and elemental compounds. The term "drug" is meant to refer to that compound whether it is in a crude mixture or purified and isolated.

As used herein, heterologous or foreign DNA and RNA are used interchangeably and refer to DNA or RNA that does not occur naturally as part of the genome in which it is present or which is found in a location or locations in the genome that differ from that in which it occurs in nature. Heterologous nucleic acid is generally not endogenous to the cell into which it is introduced, but has been obtained from another cell or prepared synthetically. Generally, although not necessarily, such nucleic acid encodes RNA and proteins that are not normally produced by the cell in which it is expressed. Any DNA or RNA that one of skill in the art would recognize or consider as heterologous or foreign to the cell in which it is expressed is herein encompassed by heterologous DNA. Examples of heterologous DNA include, but are not limited to, DNA that encodes exogenous invertase. Heterologous DNA and RNA may also encode RNA or proteins that mediate or alter expression of endogenous DNA by affecting transcription, translation, or other regulatable biochemical processes.

As used herein, operative linkage of heterologous DNA to regulatory and effector sequences of nucleotides, such as promoters, enhancers, transcriptional and translational stop sites, and other signal sequences refers to the relationship between such DNA and such

sequences of nucleotides. For example, operative linkage of heterologous DNA to a promoter refers to the physical relationship between the DNA and the promoter such that the transcription of such DNA is initiated from the promoter by an RNA polymerase that specifically recognizes, binds to and transcribes the DNA in reading frame.

As used herein, a gene containing a heterologous transcriptional or translational or processing control region(s) refers to a nucleic acid molecule or construct that includes coding portion of a gene operatively linked to a such region derived from a different gene. A homologous transcriptional or translational or processing control region(s) refers to a nucleic acid molecule or construct that includes coding portion of a gene operatively linked to a such region derived from the same gene.

As used herein, a promoter region refers to the portion of DNA of a gene that controls expression of DNA to which it is operatively linked. The promoter region includes specific sequences of DNA that are sufficient for RNA polymerase recognition, binding and transcription initiation. This portion of the promoter region is referred to as the promoter. In addition, the promoter region includes sequences that modulate this recognition, binding and transcription initiation activity of the RNA polymerase. These sequences may be <u>cis</u> acting or may be responsive to <u>trans</u> acting factors. Promoters, depending upon the nature of the regulation, may be constitutive or regulated. A constitutive promoter is always turned on. A regulatable promoter requires specific signals to be turned on or off. A developmentally regulated promoter is one that is turned on or off as a function of development.

As used herein, regulatory sequences include, sequences of nucleotides that function, for example as transcriptional and translational control sequences. Transcriptional control sequences include the promoter and other regulatory regions, such as enhancer sequences, that modulate the activity of the promoter, or control sequences that modulate the activity or efficiency of the RNA polymerase that recognizes the

promoter, or control sequences are recognized by effector molecules, including those that are specifically induced by interaction of an extracellular signal with a cell surface protein. For example, modulation of the activity of the promoter may be effected by altering the RNA polymerase binding to the promoter region, or, alternatively, by interfering with initiation of transcription or elongation of the mRNA. Such sequences are herein collectively referred to as transcriptional control elements or sequences. In addition, transcriptional controls sequences, include sequences of nucleotides that alter translation of the resulting mRNA, thereby altering the amount of a gene product.

As used herein, a reporter gene refers to a gene that encodes a detectable product. Such genes are well known to those of skill in the art and include, but are not limited to, genes encoding fluorescent proteins, particularly the well-known green fluorescent proteins, *lacZ*, enzymes and other such reporters known to be expressible and detectable in nematodes. These genes are linked to a gene of interest whereby upon expression a detectable fusion protein is produced. For purposes herein, such fusions are exemplified using an aequorin GFP (see, Chalfie *et al.* (1994) *Science 263*:802-805; see, also U.S. Patent No. 5,741,668), but any such protein may be used. For example, GFP from *Aequorea victoria* contains 238 amino acids, absorbs blue light and emits green light; it has been cloned and its sequence characterized; various mutants are also well known. Nematode optimized codons may be selected.

As used herein, a reporter gene construct is a nucleic acid molecule that includes a reporter gene operatively linked to transcriptional control sequences. Typically the construct will also include all or a portion of a the gene of interest, which herein is *lov-1* and/or *pkd-2*, and the reporter gene will be under the control of the *lov-1* or *pkd-2* promoter and other regulatory regions. By operatively linked is meant linked whereby an in-frame fusion protein is produced upon expression of the construct and whereby the reporter gene product is active (*i.e.* produces a detectable

signal or is active). The reporter gene may be linked to the 3′ or 5′ end or in any other orientation whereby it is expressed and operates as a reporter.

As used herein, isolated, substantially pure DNA refers to DNA molecules or fragments purified according to standard techniques employed by those skilled in the art, such as those described in Sambrook *et al.* (1989) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY).

As used herein, expression refers to the process by which nucleic acid is transcribed into mRNA and translated into peptides, polypeptides, or proteins. If the nucleic acid is derived from genomic DNA, expression may, if an appropriate eukaryotic host cell or organism is selected, include splicing of the mRNA.

As used herein, cloning vehicle or vector, which are used interchangeably, refers to a plasmid or phage DNA or other DNA molecules that replicate autonomously in a host cell, and that include one or a small number of endonuclease recognition sites at which such DNA may be cut in a determinable fashion without loss of an essential biological function of the vehicle, and into which DNA may be spliced in order to bring about its replication and cloning. The cloning vehicle may further contain a marker suitable for use in the identification of cells transformed with the cloning vehicle. Markers, include but are not limited to, tetracycline resistance and ampicillin resistance.

Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or prokaryotic cells. Such expression vectors may remain episomal or may integrate into the host cell genome. Expression vectors suitable for introducing heterologous DNA into plants and into host cells in culture, such as mammalian cells and methylotrophic yeast host cells, are known to those of skill in the art. It should be noted that, because the functions of plasmids, vectors and expression vectors overlap, those of skill in the

art use these terms, plasmid, vector, and expression vector, interchangeably. Those of skill in the art, however, recognize what is intended from the purpose for which the vector, plasmid or expression vector is used.

As used herein, integrated into the genome means integrated into a chromosome or chromosomes.

As used herein, a "fragment" of a protein refers to any portion of a protein that contains less than the complete amino acid sequence of the protein but that retains a biological or chemical function of interest.

As used herein, expression vector or expression vehicle refers to such vehicle or vector that capable, after transformation into a host, of expressing a gene cloned therein. The cloned gene is usually placed under the control of (i.e., operably linked to) certain control sequences such as promoter sequences. Expression control sequences will vary depending on whether the vector is designed to express the operably linked gene in a procaryotic or eukaryotic host and may additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

As used herein, a variant of a protein refers to a protein substantially similar in structure and biological activity to either the entire protein or a fragment thereof. Thus, provided that two proteins possess a similar activity, they are considered variants as that term is used herein even if the composition or secondary, tertiary, or quaternary structure of one of the molecules is not identical to that found in the other, or if the sequence of amino acid residues is not identical.

It is also understood that any of the proteins or portions disclosed herein may be modified by making conservative amino acid substitutions and the resulting modified subunits are contemplated herein. Suitable conservative substitutions of amino acids are known to those of skill in

this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. *Molecular Biology of the Gene*, 4th Edition, 1987, The Benjamin/Cummings Pub. Co., p.224). Such substitutions are preferably, although not exclusively, made in accordance with those set forth in TABLE 1 as follows:

TABLE 1

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Comparable mutations may be made at the nucleotide sequence level.

Other substitutions are also permissible and may be determined empirically or in accord with known conservative substitutions. Any such modification of the polypeptide may be effected by any means known to those of skill in this art. Mutation may be effected by any method known to those of skill in the art, such as by chemicals or radiation, and also including site-specific or site-directed mutagenesis of DNA encoding the protein and the use of DNA amplification methods using primers to introduce and amplify alterations in the DNA template.

As understood by those skilled in the art, assay methods for identifying compounds, such as antagonists and agonists, that modulate functioning of a protein or protein or pathway, generally require comparison to a control. One type of a "control" system is one that is treated substantially the same as the system, such as a worm, exposed to the test compound except that the control is not exposed to the test compound. Another type of a control may one that is identical to the test system, except that it does not express the gene or protein of interest. In this situation, the response of test system is compared to the response (or lack of response) of the control to the test compound, when each cell are exposed to substantially the same reaction conditions in the presence of the compound being assayed.

As used herein, treatment means any manner in which the symptoms of a conditions, disorder or disease are ameliorated or otherwise beneficially altered.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, a composition refers to any mixture of two or more components. It may be solution, suspension, or any other mixture.

As used herein, biological activity refers to the in vivo activities of a compound or physiological responses that result upon in vivo administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical activity of such compounds, compositions and mixtures.

Nematodes as disease models

Nematodes serve as model organisms for the study of gene expression. *Caenorhabditis elegans* is representative of nematodes. It is a small, freeliving bacteriovorous soil nematode that is a member of the

Rhabditidae, a large and diverse group of nematodes found in terrestrial habitats. Some rhabditids are pathogenic to or parasitic on animals. In common with other nematodes, *C. elegans* develops through four larval stages (also called juveniles) that are separated by moults. The lifecycle takes about 3 days at 20 ° C.

C. elegans is only 1 mm long and can be handled in a manner similar to microorganisms, including growth on petri plates seeded with bacteria. In the laboratory, *C. elegans* is fed on *E. coli*. It has a transparent body and all somatic cells (959 female; 1031 male) are visible with a microscope.

Although it is a primitive organism, it shares many of the essential biological characteristics, including embryogenesis, morphogenesis, development and aging that are central problems of human biology. The worm is conceived as a single cell that undergoes a complex process of development, starting with embryonic cleavage, proceeding through morphogenesis and growth to the adult. It has a nervous system with a 'brain' (the circumpharyngeal nerve ring), It exhibits definable behaviors, and is capable of rudimentary learning. It produces sperm and eggs, mates and reproduces. After reproduction it gradually ages, loses vigor and dies. Its average life span is 2-3 weeks.

Adult *C. elegans* are usually self-fertilizing protandrous hermaphrodites. As a result homozygous mutant stocks can be readily generated. The hermaphrodite gonad first produces germ cells that differentiate as sperm (about 250 sperm are produced) and then produces eggs. The fecundity is determined by the sperm supply.

Nematodes, particularly *C. elegans*, is one of the most thoroughly understood of all multicellular organisms. The biology of its nervous system, which contains 302 neurons, is well-documented. Many *C. elegans* genes used have counterparts in mammals, including humans. At least half of the C. elegans genes and proteins that have been characterized have structures and functions similar to mammalian genes.

These include genes encode enzymes, proteins necessary for cell structure, cell surface receptors and genetic regulatory molecules.

Animals from man to worm have most of their protein families in common and humans frequently have four to five close analogs of a protein family member, where worms have only one. Essentially all genes and pathways shown to be important in cell-, developmental- and disease-biology have been found to be conserved between worm and human. This conservation applies to the number and type of protein families, gene structure, the hierarchy of genes in genetic pathways and even gene regulation.

A consequence of this conservation is that human genes can be inserted into the worm genome, to functionally replace the worm genes even in complex cell biological and signal transduction pathways. Conversely, key worm genes identified using genetics can be used to trigger specific biochemical processes in human cells and to serve as models for the human genes.

Genetics Nomenclature

C. elegans is diploid and has five pairs of autosomal chromosomes (designated I, II, III, IV and V) and a pair of sex chromosomes (X) that determine gender. XX is a hermaphrodite and XO is male. Males are found rarely (about 0.05% of normal lab populations). The commonest lab strain, and the designated "wild-type" strain, is called N2.

For historical reasons *C. elegans* nomenclature is different from other species. Loci have a 3-letter dash one number designation. The letters are an acronym for the phenotype and the number is consecutive. Alleles have a single or double letter followed by a number. The letter identifies the isolating laboratory. Strains have a letter(s) number designation. The letters identify the isolating laboratory (i.e. AB100 abc-1(xy1000) Strain AB100 which carries the xy1000 allele of abc-1. The chromosomal location can be added: AB100 abc-1(xy1000) I. Multiple mutant alleles carried in one strain are organized by chromosome,

and chromosomes separated by semicolons. Heterozygous nematodes are designated by a abc-1/+ notation. Hence abc-1(+) indicates the wild-type (N2 strain) copy of the gene. Proteins are capitalised and not italicized. ABC is the protein product of abc-1.

Rearrangements, duplications and deficiencies have a letter prefix (indicating the isolating lab) a Dp (pronounced dupe, for duplication) or Df (pronounced dif for deficiency) and a number (*i.e.*, xyDp1 is duplication number 1 from xy and xyDf1 is deficiency number 1 from xy lab). Transgenic strains carrying the transgene as a free extrachromosomal array are designated as follows: xyEx1[abc-1(+)] is a transgenic strain carrying the wt copy of abc-1.

The C. elegans Genome

The *C. elegans* genome, which is 97 Mb, contains six approximately equally sized chromosomes (5 autosomes, one X) and it has been sequenced (see,(1998) *Science 282*:2012-2018) and is publicly available. The 97 Mb encodes a predicted 19,099; although as shown herein, there remain ambiguities. Over 60,000 cDNA fragments have been tag sequenced and 101000 ESTs deposited. These "expressed sequence tags" or ESTs offer a set of snapshots of gene expression in the nematode, and have identified around half of the organism's genes. The cDNA data is used in the prediction of genes from the genome sequence along with database searches for similarities between *C. elegans* genes and those of other organisms such as humans. This estimate is based on the correspondence between genomic DNA sequence and cDNA sequences, and on the prediction of coding genes from genomic sequence.The genome data (and much else besides) is collated into an available database ACeDB, written for the *C. elegans* project. A physical map of the genome, which is publically available in the *C. elegans* genome database ACeDB, has been constructed. The map is based on 17,000 cosmid clones of genomic DNA (insert size 35-40 kb). These clones were "fingerprinted" using restriction enzymes, and the

fingerprints used to order the clones in overlapping contiguous sets, or contigs. These cosmid contigs have been supplemented by a set of 3,000 yeast artificial chromosome clones (insert sizes 100 kb and above). Because the yeast host tolerates sequences that *E. coli* does not, the YAC clones can "bridge" gaps between contigs of cosmids. With these two resources, contigs covering >95% of all the chromosomes have been assembled. The clones are freely available for researchers, and the 3,000 YAC clones are available as an array on a filtermat, arranged in approximate chromosomal order, for screening purposes.

The genomes of other nematodes are in the same size range. *Brugia malayi*, a filarial parasite of humans, has a genome of 100 Mb; *Ascaris suum*, the pig roundworm, has a larger germ line genome which undergoes somatic diminution.

Identification of the genes associated with the location of vulva and response behaviors

The behaviors

The six sub-steps of the stereotyped copulatory sequence has been correlated with the function of individual neurons, and behavioral mutants have been isolated (Liu *et al. Neuron 14*:79-89). *C. elegans* male mating behavior includes a series of steps: response to contact with the hermaphrodite, backing along the body of the hermaphrodite, turning around her head or tail, location of the vulva, insertion of the two copulatory spicules into the vulva and sperm transfer. Sensory structures and neurons that participate in each of these steps have been identified: the sensory rays mediate response to contact and turning; the hook, the postcloacal sensilla and the spicules mediate vulva location; and the spicules also mediate spicule insertion and regulate sperm transfer.

Thus, the stereotyped mating behavior of the *Caenorhabditis elegans* male comprises several substeps: response backing, turning, vulva location, spicule insertion, and sperm transfer (Fig. 1). The complexity of male mating behavior is reflected in the sexually dimorphic

anatomy and nervous systems of the male and hermaphrodite (Hodgkin, J. (1988) in *The Nematode C. elegans* (ed. Wood, B.) pp. 243-279 (Cold Spring Harbor Laboratory Press, New York). Behavioral functions have been assigned to most male-specific sensory neurons via cell ablations (Liu *et al. Neuron 14*:79-89). Although the hermaphrodite is behaviorally passive, her vulva provides sensory cues to the male.

Vulva location behavior is complex. The male stops and precisely positions his tail over the vulva, coordinates his movement to the hermaphrodite's, and ultimately insert his spicules into the vulva slit and transfers sperm into the uterus. The hook sensory neurons, HOA and HOB, are specifically required for location of vulva (Lov) behavior. Ablation of either HOA or HOB results in a Lov defect whereby the ablated male circles the hermaphrodite without stopping at the vulva (Fig. 1). Eventually, the ablated male begins an alternative search by backing slowly and prodding randomly with his spicules until the vulva is located. The postcloacal sensilla are required for slow search behavior. Vulva location behavior is executed by a minimum of eight sensory neurons with overlapping and redundant functions (Liu *et al. Neuron 14*:79-89).

A genetic analysis of vulva location behavior to investigate how genes specify sensory behavior, beginning with sensory reception was performed. The mating behavior of existing mutants defective in sensory behaviors including chemotaxis to soluble and volatile odorants, mechanosensation, and osmotic avoidance was first examined. From this survey, it was found that only males with severe defects in all sensory neuron cilia (*osm-4, osm-5, osm-6*, and *che-3*) were Lov defective (Table 2). For example, *osm-6(p811)* males locate the vulva with an efficiency of 32% versus 96% of wild-type (Table 2). These males are also response defective, but not so severely as to prevent observation of the Lov phenotype. The only ciliated cells in *C. elegans* are chemosensory and mechanosensory neurons (White *et al.* (1986) *Philos.*

Trans. R. Soc. Lond. B Biol. Sci. 314:1-340). The male tail possesses thirty predicted ciliated sensory neurons (Sulston *et al.* (1980) *Dev. Biol. 78*:542-576), consistent with the observation that ciliated neurons modulate response and Lov. *osm-6::gfp* is expressed exclusively in ciliated neurons, with male-specific expression in four CEM head neurons and neurons of the rays and copulatory spicules (Collet *et al.* (1998) *Genetics 148*:187-200). More detailed examination revealed that *osm-6::gfp* expression begins at the L4 stage in neuronal cell bodies and extends to dendrites as neuronal outgrowth proceeds (data not shown). The RnA and RnB neurons of each ray (ray 1 through ray 9), the HOA and HOB hook neurons, the spicule neurons SPV and SPD, and the PCB postcloacal sensilla neurons accumulate GFP. The *osm-6* expression pattern and mutant phenotypes indicate that OSM-6 might be required for the structure and function of ciliated neurons in the adult male tail. In the hermaphrodite, *osm-6* function is required for nose touch (Kaplan *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A. 90*:2227-2231), osmotic avoidance, chemotaxis, dye-filling of sensory neurons, thermotaxis, dauer formation, and proper assembly of ciliated sensory endings (Perkins *et al.* (1986) *Dev. Biol. 117*:456-487). Hence, ciliated endings are important for all known sensory behaviors, including Lov.

TABLE 2. Vulva location behavior of wild-type and mutant males

Genotype	vulva location efficiency %	Significantly different from wild-type (p value)		†n
him-5 (wild-type)	96	—	—	101
osm-1(e1803)	65	No	(0.0738)	
osm-4(p821)	48	Yes	(0.0004)	
osm-5(p813); him-5	26	Yes	(0.0002)	
osm-6(p811)	32	Yes	(0.0003)	
che-3(e1124)	69	Yes	(0.02666)	
lov-1(sy582Δ)	11	Yes	(<0.0001)	
lov-1(sy582); him-5	30	Yes	(<0.0001)	

Table 2. *lov-1(sy522); him-5(e1490), lov-1(sy582Δ)*, and all cilia defective mutant were also response defective. Males that eventually responded were scored for Lov behavior. [†]**n** represents the number of males observed, each for a minimum of 10 vulva encounters per male. Mann-Whitney tests determined p values. The following non-cilia-defective osmotic avoidance (*osm*), mechanosensory defective (*mec*), chemosensory defective (*che*), odorant response abnormal (*odr*) and dauer formation defective (*daf*) mutants were also examined and found to be normal for response and Lov behavior: *osm-3(e1806); him-5(e1490), osm-7(n1515), osm-8(n1518), osm-10(n1604),osm-11(n1604), osm-12(n1606), mec-3(e1338) him-8(e1489), mec-4(e1611), mec-5(e1340), mec-7(n434), mec-7(e1343), mec-8(e398), mec-9(e1494), che-112, odr-1(n1936), odr-2(n2145), odr-3(n2150), odr-4(n2144ts), odr-5, odr-6(kyl), odr-7(ky4, odr-10(ky32)* and *daf-11(m47ts).*

Provided herein are mutants that are defective in location of the vulva (Lov). Lov mutant males are unable to execute this step. In addition, these males are also defective in the first sub-step, 'response'. Response and vulva location depend on two types of male sensory structure: the first is a set of nine pairs of rays, which project out of the tail on each side; and the second is a hardened cuticular structure called the hook, which contains two sensory neurons. These mutants were used to identify the genes involved in these behaviors.

Identification and cloning of the lov-1 gene

To elucidate the molecular basis of behavior and sensory the mutants are studied and genes associated with the behaviors are identified. A gene designated *lov-1* that is required for two male sensory behaviors, response and location of vulva (Lov) is described herein. It is also associated with other sensory behaviors controlled by the CEM neurons.

This gene, *lov-1*, encodes a putative membrane protein with a mucin-like, serine-threonine rich amino terminus (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44) followed by two blocks of homology to human polycystins encoded by the autosomal dominant polycystic kidney disease (ADPKD) genes (Torres *et al.* (1998) Current Opinion in Nephrology and *Hypertension* 7:159-169). LOV-1 and human PKD1 are 26% identical in block 1. Block 2 also shows 20% identity between LOV-1, all identified polycystins (PKD1, PKD2, and PKDL), and the family of voltage-activated channels (Torres *et al.* (1998) Current

Opinion in Nephrology and *Hypertension* *7*:159-169). Overall, LOV-1 is the closest *C. elegans* homolog of PKD1. The polycystin/channel domain (block 2) of LOV-1 is required for function. *Lov-1* is specially expressed in adult male sensory neurons of the rays, hook, and head, mediating response, Lov, and potentially chemotaxis to hermaphrodites, respectively (Liu *et al. Neuron 14*:79-89, Ward *et al.* (1975) *J. Comp. Neurol. 160*:313-337). Localization of *lov-1* to neuronal cell bodies and ciliated sensory endings is consistent with a role in either chemo- and/or mechanosensory reception and signaling. Human PKD proteins might similarly be involved in sensory reception during osmoregulation, organogenesis and/or organ maintenance.

Cloned genes and encoded proteins

To identify genes specifically required for male sensory behaviors, mutants defective in Lov were screened. *Lov-1(sy552)* males have specific response and Lov defects. Upon encountering a hermaphrodite, a *lov-1(+)* male ceases forward motion, places his tail flush on the hermaphrodite, commences backing along her body, and turns at her ends until he encounters her vulva and stops. Mutant males defective in *lov-1* frequently do not respond to contact with the hermaphrodite and continue blindly moving forward. When response is initiated, *lov-1* mutants back and turn normally but pass the vulva at a high frequency. The response and vulva location ability of *lov-1(sy552)* is 30% that of *lov-1(+)* males (Table 2). Spiculte insertion and sperm transfer behaviors are unaffected. *lov-1(sy552)* males exhibit high mating efficiency with severely paralyzed *unc-52* hermaphrodites but sire few progeny with actively moving *dpy-17* hermaphrodites. Differences between mating efficiencies is partner-dependent. A paralyzed partner is an easier target for the *lov-1* mutant male who is defective in response and Lov but unimpaired in the behaviors of backing, turning, spicule insertion, and sperm transfer. The behavioral defects of *sy552* are limited to male mating. *Lov-1(sy552)*

mutants appear normal for other sensory behaviors including egg laying, nose touch, tap, mechanosensation, and osmotic avoidance.

The *lov-1* gene was cloned by genetic mapping and transformation rescue of the *sy552* behavioral defects (Fig. 2a). *mnDf2l/sy552, mnDf83/sy552* and *sy552/sy552* males are phenotypically indistinguishable; therefore, *sy522* is reduction or loss of function mutation in *lov-1*. This conclusion is supported by the observed recessive nature of *sy552*. A 16.9 kb HindIII subclone (plov-1.1) of the cosmid ZK945 rescued response and Lov defects of *sy552* (Fig. 2a). Both a 6.7 kb HindIII-BamHI fragment from plov-1.1 (plov-1::GFP1) and a 14.1 kb HindIII-StuI frameshift in plov-1.1 (plov-1.3) fail to rescue *sy552* defects (Fig. 2b) yet act in a dominant negative (DN) manner in wild-type males with respect to Lov behavior (Fig. 2c). Wild-type males expressing either plov-1::GFP or plov-1.3 are Lov defective. These transgenic males exhibit a wild-type response to hermaphrodite contact. Without being bound by a theory, the differences in *sy552* and transgenic DN phenotypes might be attributed to dosage or mosaicism.

Figure 2b illustrates the intron-exon boundaries of the *lov-1* gene. Using RT-PCR with *lov-1* specific primers and *him*-5 mRNA, it was found that *lov-1* encodes one transcript corresponding to Genefinder-predicted ORFs, ZK945.10 and ZK945.9 (Fig. 2b), which had been thought to be two genes. *Lov-1* encodes a predicted 3178 amino acid membrane-bound protein (see SEQ ID Nos. 3 and 4) with a serine-threonine rich extracellular domain homologous to mucins (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44), a polycystin homology block 1 (26% identity), and a carboxy terminal polycystin block 2 with 20% identity to polycystin proteins 1, 2, and 2, encoded by the PKD1, PKD2, and PKDL (polycystic kidney disease) genes, respectively (Fig. 2d). A Kyte-Doolittle hydropathy plot predicts multiple transmembrane domains; although no signal peptide is predicted in LOV-1. Mucins are highly glycosylated extracellular proteins thought to serve cell adhesion

and/or protective functions (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44).

Similarity between exons W (for PKD1 only), X, Y, Z, AA, BB, and CC of *lov-1* and PKD1, PKD2, and the family of voltage-activated calcium and potassium channels in the six transmembrane spanning region has been observed (Mochizuki *et al.* (1996) *Science 272*:1339-1342). This extends to PKDL (Nomura *et al.* (1998) *J. Biol. Chem. 273*:25967-25973). LOV-1 lacks the Ca^{2+} binding EF-hand of polycystin 2 and L, and a coiled-coil domain of all three polycystins (Fig. 2d), which has been shown to mediate hetero- and homotypic interactions between polycystin 1 and polycystin 2 (Qian (1997) *Nature Genetics 16*:179-183; Tsiokas *et al.* (1997) *Proc. Natl. Acad. Sci. USA 94*:6965-6970). Block 2 also shows limited homology with the trp (transient receptor potential) family of channels (Montell *et al.* (1989) *Neuron 2*:1313-1323). The critical difference between voltage-gated and trp channels is the presence of a positively charged S4 transmembrane domain that acts as a voltage sensor (Montell *et al.* (1989) *Neuron 2*:1313-1323). LOV-1 more closely resembles voltage-gated channels in this respect. A frameshift disruption in *lov-1* (plov-1.3) one residue away from a corresponding nonsense mutation in human PKD2 (Mochizuki *et al.* (1996) *Science 272*:1339-1342) destroys the ability to rescue *lov-1(sy552)*, as mentioned above. The construct plov-1.3 encodes a truncated protein lacking the polycystin block 2/channel domain. These results demonstrate that the polycystin block 2/channel domain is essential for LOV-1 function, and indicate that functional as well as structural similarities might exist between LOV-1 and PKD-2. LOV-1 also possesses a nucleotide-binding domain (Fig. 2d) that is not present in the human polycystins. The structure of LOV-1 is also indicative of a role in signal transduction.

The *lov-1* gene product appears to be a membrane spanning protein that includes an extracellular domain with a serine/threonine-rich mucin-like domain, an ATP-binding domain, and small cytoplasmic tails that mediate interaction with other members of the pathway, including a *pkd-2* gene product that is also a membrane spanning protein, with six membrane domains, and a cytoplasmic EF-hand. Interaction of these proteins lead to the observed phenotypic response. In *c. elegans* this response can be detected as a clearly identifiable phenotype. Hence, *c. elegans* and mutants thereof can serve as a test system for identifying compounds that alter this pathway and also for identifying other gene products involved in the pathway.

lov-1 gene

In an exemplary embodiment, the complement of the nucleic acid sequence of the *lov-1* gene from *C. elegans* is provided. Corresponding genes from other nematodes may be identified, such as by using the nucleic acid provided herein and screening an appropriate library, genomic or cDNA library, using standard procedures. Alternatively, databases of sequence may be searched and the genes from other nematodes homologous to those provided herein identified, again using standard searching and alignment programs.

SEQ ID NO. 3 is the complement of the genomic sequence of the *lov-1* gene. It includes open reading frames (ORFs) between nucleotides 15760 to 27880 of cosmid ZK945 (nucleotides 1 to 12121 of SEQ ID NO.3) and nucleotides 1-564 of cosmid F27E5 (nucleotides 12122 to 12685 of SEQ ID NO.3). It was found herein, however, that ZK945 and F27E5 overlap from nucleotides 27881 to 27981 and nucleotides 1 to 101, respectively (the overlap region includes nucleotides 12122 to 12222 in SEQ ID NO.3), thereby providing a single, rather than two, ORFs.

It been thought that the open reading frame in cosmid ZK945 (the "ZK945.9" gene; nucleotides 1 to 9164 of SEQ ID NO.3), and the open

reading from in cosmid F27E5 (the "ZK945.10" gene; nucleotides 9415 to 12685 of SEQ ID NO.3) encoded two genes. DNA sequence analysis of RT-PCR generated cDNA clones from *him-5(e1490)* RNA revealed three exons (**exons I, J and K** in Figure 2B) in the junction between ZK945.10 and ZK945.9: one from nucleotides 25195 to 25742 of the ZK945 cosmid (nucleotides 9436 to 9983 of SEQ ID NO. 3); a second from nucleotides 25071 to 25151 of the ZK945 cosmid (nucleotides 9312 to 9392 of SEQ ID NO. 3); and a third initiating at position 25021 in the ZK945 cosmid (nucleotide 9262 of SEQ ID NO. 3). This demonstrated that the *lov-1* gene encodes one large transcript corresponding to ORFs in ZK945.10 and ZK945.9, spanning what had previously been thought to encode two proteins.

As noted above, Figure 2B depicts the *lov-1* genomic structure (exons shown as boxes, introns as lines). With reference to Figure 2B, the coding sequence in the gene set forth in SEQ ID No. 3 (noting that SEQ ID 3 sets forth the non-coding strand) is as follows:

Complement (Join (12500...12685) - Exon A; (12266...12451) - Exon B; (12085...12217) - Exon C; (11683...11823) - Exon D; (11498...11637) - Exon E; (11128...11452) - Exon F; (10268...10899) - Exon G; (10138...10216) - Exon H; (9436...9983) - **Exon I**; (9312...9392) - **Exon J**; (8685...9262) - **Exon K**; (8557...8635) - Exon L; (7830...7997) - Exon M; (6774...7786) - Exon N; (6648...6728) - Exon O; (6305...6598) - Exon P; (6006...6255) - Exon Q; (5732...5958) - Exon R; (4849...5076) - Exon S; (4698...4799) - Exon T; (4383...4651) - Exon U; (3336...4328) - Exon V; (2229...3094) - Exon W; (1976...2181) - Exon X; (1635...1930) - Exon Y; (1043...1591) - Exon Z; (625...999) - Exon AA; (329...572) - Exon BB; (1...270) - Exon CC).

The LOV-1 amino acid sequence is set forth in SEQ ID NO. 4 The following table summarizes the above.

TABLE 3 Comparison of Sequence ID No. 3 with source Cosmids†

EXON	SEQ ID 3	ZK945	F27E5
A	12500..12685		379..564
B	12266..12451		145..330
C	12085..12217	27844..27976	
D	11683..11823	27442..27582	
E	11498..11637	27257..27396	
F	11128..11452	26887..27211	
G	10268..10899	26027..26658	
H	10138..10216	25897..25975	
*I	9436..9983	25195..25742	
*J	9312..9392	25151..25071	
*K	8685..9262	24444..25021	
L	8557..8635	24316..24394	
M	7830..7997	23589..23756	
N	6774..7786	22533..23545	
O	6648..6728	22407..22487	
P	6305..6598	22064..22357	
Q	6006..6255	21765..22014	
R	5732..5958	21491..21717	
S	4849..5076	20608..20835	
T	4698..4799	20457..20558	
U	4383..4651	20142..20410	
V	3336..4328	19095..20087	
**W	2229..3094	17988..18853	
X	1976..2181	17735..17940	
Y	1635..1930	17394..17689	
Z	1043..1591	16802..17350	
AA	625..999	16384..16758	
BB	329..572	16088..16331	

EXON	SEQ ID 3	ZK945	F27E5
CC	1..270	15760..16029	

*exons I, J, K at the junction of ZK945.10 and ZK945.9 (as determined by RT-PCR analysis, and not predicted by the GeneFinder program)

**the *sy582* lov-1 mutant has a 1059 bp deletion beginning in exon W at position 2267 of SEQ ID NO. 3 (18026 of the ZK945 cosmid) and ending at position 1209 of SEQ ID NO. 3 (16968 of the ZK945 cosmid).

† The GenBank accession numbers for ZK945 and F27E5 are (GenBank Accession No. Z48544) and (GenBank Accession No. Z48582), respectively.

Exemplary knockout mutant *sy582*

A genomic deletion of *lov-1* in a PCR screen of EMS mutagenized worms was isolated. *lov-1(sy582Δ)* encodes a truncated protein lacking the polycystin/cation channel homology domain (Fig. 2d). Like *sy552, lov-1(sy582Δ)* males exhibit defects in response and Lov behaviors (Table 2), as well as low mating efficiency with *dpy-17* but not *unc-52* partners. *sy582*Δ is recessive and fails to complement *sy552.* The truncated protein produced by *lov-1(sy582Δ)* does not act as a dominant negative in contrast to the truncated protein produced by plov-1.3 (see below). This difference might be due to a dosage effect of the plov-1.3 transgene. These results confirm that the polycystin block 2/cation channel domain is essential for LOV-1 activity and indicate that *lov-1(sy582Δ)* is completely defective in LOV-1 function.

The *lov-1* (*sy582*) mutant is a 1059 bp deletion of nucleotides 18026 to 16968 of ZK945 (nucleotides 2267 to 1209 of SEQ ID NO. 3). The deletion, which begins in exon W, removes the majority of the PKD homology block 2 (a total of 308 amino acids, beginning at amino acid 2520 and ending at amino acid 2827 of the sequence set forth in SEQ ID NO. 4) and continues to read in-frame to the end of the sequence set forth in SEQ ID NO. 4. This results in a protein of 2870 amino acids with the amino acid sequence set forth in SEQ ID NO. 15.

Other mutants may be prepared by any method known to those of skill in the art, including directed mutagenesis of the gene in a selected

nematode or random mutagenesis and selection for the altered male mating behavior in the lov and/or response, preferably both behaviors. Preferred regions for deletion include the exon A. Precise size of the deletion and or locations to delet can be determined empirically using standard routine methods based upon the disclosure herein, which identifies the gene and the resulting phenotype. Other mutations including insertions and point mutations that alter these behaviors are also contemplated and can be readily prepared.

Expression patterns of *lov-1*

To elucidate the cells in which *lov-1* acts to affect male mating behaviors, the expression pattern of *lov-1*-::GFP reporter genes was examined (see Example 2 and Fig. 4). These experiments reveal regulatory regions in the *lov-1* gene. A partial translational fusion containing 2.8 kb of upstream sequence and 3.9 kb of *lov-1* (plov-1::GFP1) directs male-specific expression in male-specific sensory neurons (Fig. 2c and Fig. 4). Conversely, shorter versions of plov-1::GFP1 are not expressed in the same set of male-specific neurons nor exclusively in male-specific sensory neurons and do not act as DNs (Fig. 2c). Similar results were observed with pkd-2 mutants (see Example 2 and Fig. 4).

Nematode pkd-2

A search for a homolog of *LOV-1* was performed to ascertain whether nematodes possess a PKD2 ortholog. A BLAST search of the Sanger Center *C. elegans* genome data base revealed a possible *LOV-1* homolog, Y73F8A.B. This cosmid encodes a protein with 27% identity to PKD2 and possesses the coiled-coil domain of all polycystins. It is shown herein that Y73F8A.B and Y73F8A.A encode one transcript that is the *C. elegans* ortholog of human PKD2 (Fig. 2d and Fig 3). The resulting nematode gene, designated *pkd-2*, cDNA and encoded protein are provided herein.

The *C. elegans* gene is exemplified herein. SEQ ID No. 5, which sets forth the complement of the coding strand, is provided. It contains nucleotides 1605 to 9677 of *C. elegans* cosmid Y73F8A (GenBank Accession No. AL132862), which correspond to nucleotides 1 to 8073 of SEQ ID No. 5. The sequence of the encoded protein is set forth in SEQ ID No. 6. Figure 3B shows *pkd-2* genomic structure (exons shown as boxes, introns as lines). The cDNA yk219e1 was sequenced and corresponds to the 3' end of pkd-2.

Figure 3B shows the *pkd-2* genomic structure (exons shown as boxes, introns as lines). The coding sequence in the gene set forth in SEQ ID No. 5 is produced as follows:

Complement (Join (7980...8073) - Exon 1; (7396...7585) - Exon 2; (6765...7045) - Exon 3; (5153...5283) - Exon 4; (4863...5104) - Exon 5; (3931...4158) - Exon 6; (2875...3424) - Exon 7; (1957...2208) - Exon 8; (1542...1795) - Exon 9; (367...505) - Exon 10; (1...87) - Exon 11.

As discussed above, the architecture of *LOV-1*, including a large extracellular amino terminus, Block 1, and Block 2, is similar to that of human PKD1; the architecture and sequence of *PKD-2* is similar to PKD2. Taken together, LOV-1 and PKD-2 appear to be part of a multi-component complex and pathway. Further genetic analysis of Lov behavior confirms this.

Knockout mutation of pkd-2

A knockout mutation can be prepared by any method known to those of skill in the art. A deletion mutant, designated *sy606* was produced (see, Examples for primers used). A 2397 bp deletion from nucleotides 8338 to 5942, starting in intron 3 and ending in intron 5, removing exons 4 and 5 (including the partial transmembrane spanning domain S1 and the polycystin motif) with the new splice in a different reading frame resulting in a stop codon (TGA) at 5736, produced a knockout mutation. The resulting phenotype was the same as that resulting from a knockout of *lov-1*, thereby demonstrating that the two

proteins are part of the same pathway that results in the observed phenotype.

The *pkd-2* (*sy606*) mutant contains a 2397 bp deletion of nucleotides 8338 to 5942 of Y73F8A (nucleotides 6734 to 4338 of SEQ ID NO. 5), starting in intron 3 and ending in intron 5, removing exons 4 and 5 (including the partial transmembrane spanning domain S1 and the polycystin motif) with the new splice in a different reading frame. This results in a stop codon (TGA) at nucleotide 5728 (nucleotide 4124 in SEQ ID NO. 5). The sequence of the protein encoded by the *pkd-2* deletion mutant (*sy606*) is set forth in SEQ ID NO. 16.

TABLE 4
Comparison of Sequence ID No. 5 with source Cosmid

EXON	SEQ ID 5	Y73F8A
1	7980..8073	9584..9677
2	7396..7585	9000..9189
3	6765..7045	8369..8649
4	5153..5283	6757..6887
5	4863..5104	6467..6708
6	3931..4158	5535..5762
7	2875..3424	4479..5028
8	1957..2208	3561..3812
9	1542..1795	3146..3399
10	367..505	1971..2109
11	1..87	1605..1691

**the *sy606* pkd-2 mutant has a 2397 bp deletion of nucleotides 8338 to 5942 of Y73F8A (GenBank Accession No. AL132862; nucleotides 6734 to 4338 of SEQ ID NO. 5), starting in intron 3 and ending in intron 5, removing exons 4 and 5, with the new splice being in a different reading frame and resulting in a stop codon (TGA) at nucleotide 5728 (4124 in SEQ ID NO. 5).

Other such deletions may be similarly produced by deleting any portion that eliminates at least one of the observed phenotypic behaviors associated with the *lov-1* and *pkd-2* pathway. Preferable targets for these deletions are those that destroy reading frame resulting in non-

functional truncated proteins, deletions that eliminate transcriptional or translational control regions, deletions in the first exon or exon such that the deletion (or insertion or point mutation) eliminates or substantially attenuates activity of the encoded protein as evidenced by altered phenotype.

The lov-1 and pkd-2 genes encode homologs of the polycystins

It is shown herein that the *lov-1* and *pkd-2* genes and gene products are homologs of mammalian polycystins, particularly PKD1 and PKD2, respectively. As such nematodes that express these genes, and/or mutants of the genes can serve as models to study the expression of the genes, the function of these genes, to identify additional genes in the pathway, and for screening for compounds that will serve as lead compounds for treatment of PKD in mammals, particularly humans.

Neither the precise functions of the polycystins nor the molecular basis of kidney cystogenesis is known. The results provided herein show that the homologs of the polycysins act together in a pathway, that appears to be a signal transduction pathway, in sensory neurons. It has been postulated that human polycystin 1 and polycystin 2 function as an ion channel (Torres *et al.* (1998) Current Opinion in Nephrology and *Hypertension* 7:159-169). Further supporting this conlusion, are the results of others that have indicated that human PKD2 is associated with the activity of a cation channel. These results were obtained using cell-expression and electrophysiological approaches to examine the potential channel function of a protein called PCL (polycystin-like) that had been identified in the human expressed sequence-tag database by its sequence similarity with PKD2 (Chen *et al.* (1999) *Nature 401*:383-386). PCL was expressed in *Xenopus oöcytes* by microinjecting synthetic mRNA and the channel properties were studied using the the two micro-electrrode voltage clamp and patch-clamp techniques. It was found that PCL is a non-selective cation channel that is permable to sodium, potassium and

calcium. It is more permeable to calcium. Thus, PCL and PKD2 may be cation-channel subunits.

Hence, as shown herein, PKD1-related proteins act as receptors that regulate the activity PKD2-related proteins. The two proteins are part of a conserved pathway that appears to be a signalling mechanism in which the translocation of ions acts as a second messenger.

Exemplary strains

Strains that exhibit one or more of the behaviors are provided. The strains may be prepared by mutagenizing wild-type or other strains with other desirable characteristics and selecting for those with the behavioral phenotype.

Strain PS3152 is an N2 strain with a deletion in lov-1 (*lov-1(sy582)*)

Strain PS2816 has the *lov-1(sy552)* deletion in a background with a him-5 (high incidence of males) and plg-1, which is a mutation that causes the male to use a gelatinous mating plug (which can be used to visualize mating).

Strain PS2817 is a paralyzed (unc-52) version of PS2816.

Strain PS3150 has the same deletion in a background with a him-5 (high incidence of males) and ts lethal marker (*pha-1*). A strain with a ts marker is a good recipient for transformation.

strain recipient for transformation - *pha-1* marker - , any marker can be

PS3151 is the same as PS2815 without the *plg-1*

PS3149 has a *pha-1* marker, in a *him-5* bacground and and transforemed with an extrachromosomal element containing a *lov-1::GFP1* construct and *pha-1(+)* DNA.

Anbother strain is an *him-5* strain with the *lov-1(sy582)* deletion.

PS3400 has a deletion mutation in pkd-2, it is *pkd-2(sy606)*.

PS3401 is a *him-5* strain with the *lov-1(sy582)* deletion

PS3377 is *pkd02(sy606)* in a *him-5* background.

These and other strains may be used in the assay methods described herein or in any assay that assesses the pathways and sensory functions which *lov-1* and/or *pkd-2* are involved or that can be used for identifying compounds that affect this pathway(s).

Assays for screening compounds and for identifying mutants with observable Lov and/or response defective behavior

Assays for identifying additional genes in the pathway, to assess the activities of proteins in the pathway, to identify regulators of gene expressions and factors involved in gene expression of genes in this pathway, and for screening for compounds that affect polycystin function are provided. Compounds that affect polycystin function in a nematode are candidates for further investigation and serve as leads for compounds that may be therapeutically useful for treating mammalian PKDs.

Identification of components of the PKD pathway will aid in understanding the etiology of the disease and permit identication of disease markers and defective genes, thereby permitting development of reagents for diagnostic tests and identification of therapeutic targets and therapeutic agents.

The assays may be adapted for high throughput methods, particularly by using multiwell plates, such as 24, 96, 384 wells or higher densities, and automating many of the steps. By using multiple wells, for example, many compounds can be screened. The results can be automated by using video or other recording means to record the behavior in each well. Viewing using such means is facilitated by visually labeling the animals, such as by introduction of reporter gene constructs that will be expressed in areas of interest, such as the vulval and tail region of the hermaphrodite, to render the animal visible to a camera. If a GFP is used, for example, the camera will be equipped with an appropriate filter to screen out all but the green glow. Other ways of making the animals visibile, include, for example, use of plg-1 animals, which leave a visible gelatinous trail as they move through the agar.

Precise protocols for culturing and nematodes, producing mutants and transgenics, and for observing behaviors are well known to those of skill in the art.

Assays using wild-type males

Behavioral screens

In these assays males will be identified that exhibit abnormal behavior, particularly abnormal Lov and/or response behaviors, therby detecting components of PKD function, signaling or regulators, or identifying compounds that are candidates for afecting PKD function, signaling or regulation. A behavioral assay is depicted in Fig. 1, and described herein.

The tests are performed by placing male nematodes on an agar surface, such as a petri dish or microtiter plate with an agar surface, that is seeded with anything, including bacteria or chemoattractants, such as NaCl, that will keep the males in a field of view. One or more mating partners, such as a hermaphrodite, is placed on the plate and the behavior is recorded, such as by direct observation, review of a video tape, or any method whereby the behavior can be recorded.

For example, observations of the behaviors can be observed using young adult hermaphrodites, such as *unc-31(e169)* hermaphrodites, on a lawn of bacteria, such as *E. coli*. The use of *unc-31* hermaphrodites, which are sluggish, makes it easier for males to keep pace with them.

For drug screening assays, the effects of a test compound are examined. The males are treated with a compound, such as by culturing them in the presence of the compound., or including the compound in the mating dish, or pretreating the males with the compound. For analysis of mutants, males from parents or grandparents that had been mutatagneized with chemical and/or radiation are tested.

In either embodiment, the behavior of the males is observed by looking for one or both, preferabl both, of the Lov and 'response' behaviors compared to controls, untreated males for the drug screening

assays or wild-type for the mutant assays. If behavior of the treated males differs from controls, then the compound has some activity and is selected for further analysis.

For the assays of mutants, if the behavior of the males differs from the controls, the mutation(s) are identified, such as by mapping. The mutant gene is then identified, genetically analyzed and its role in the pathway elucidated.

These methods as well as the others provided herein can be adapted for high throughput analysis, including automation, such by videotaping and image processing. For image processing the animals can be visually labeled, such as by expressing, a reporter gene, like GFP, to produce stable transgenic strain of some construct of GFP with any promoter that would direct expression with sufficient intensity or in a sufficient number of cells to visualize the behavior. For example, a glowing vulva and tail would permit visualization of the Lov and response behaviors. Suitable genes for linkage to a reporter are any that are expressed in the the animal to permit such visualization. Such markers include, but are not limited to, autofluorescence of the male spicule, egl-5-gfp, and of the hermaphrodite vulval region lin-11-gfp.

Measurements can be performed by any method known to those of skill in the art (see, *e.g.*, Liu *et al.* (1995) *Neuron 14*:79-89). Briefly, measurements can be are obtained as follows: time is kept with a stopwatch or key stroke recorder on a computer to record an 'ethogram', and distances estimated by eye and confirmed from microgaphs taken of the behavior. Mating behavior is sensitive to a number of variables, including the moisture level of the plates, which are not used if they are more than a week old, hermaphrodite age. Hence controls and test animals are carefully matched. At least three hermaphrodites are used per male to control for hermaphrodite specific behaviors.

Mating efficiency assays

As noted above, deletion of lov-1 compromises but does not abolish the ability to mate. The mutant male can mate with paralyzed or moving impaired partners. To perform these assays, wild-type males are treated with a test compound or mutagenized, and males that sire fewer cross-progeny compared to wild-type or cannot sire cross-progeny with moving partners are identified.

To detect whether the progeny are those of the males rather than the hermaphrodites, sperm defective hermaphrodites can be used. Preferably the hermaphrodites are temperature-sensitive (ts) sperm defective. Alternatively, the mating can be detected the mating by using a visual marker, such as using short and fat (Dpy;Dumpy) hermaphrodites, or males that express a visually or otherwise detectable transgene, such as fluroescent proteins (FPs), including, but not limited to blue fluroescent proteins and green fluorescent proteins (GFPs), and looking for the transgene in progeny could have a transgene transferred into the progeny by the mating and detectable. If a FP is used as a marker, glowing offspring are detected.

Progeny can also be detected by measuring the density of the resulting culture and a ts sperm defective hermaphrodite. If there are lot of progeny, it can be inferred that the males have mated, since the hermaphrodite is sperm defective.

Assays using mutant males

Suppressor and enhancer genetics can be used to assign functions to genes, to assign genes to pathways, to identify the key switches in these pathways and to provide a sensitive assay to identify new genes in a pathway and lead compounds that modulate the activity of genes and/or gene products in the pathway.

Suppressor screen In these assays, the process starts with a *lov-1* mutant and restoration of one or both behaviors is assessed, thereby identifying compounds or mutations that restore the defect. Restoration can occur, for example, by by-passing the defective gene, such as constitutive expression of a gene further down the pathway that had previoulsy required *lov-1* or *pkd-2* activity. Alternatively, a mutation could knock-out the activity of another gene that suppresses the activity of *lov-1* or *pkd-2*, thereby restoring the pathway. These assays will identify other genes in the pathway. These assays can also identify a compound that corrects defect in the pathway, thereby providing a promising therapeutic lead for treatment of APKD.

Enhancer screen In these assays, the defect is exacerbated by looking for mutations or compounds that increse the penetrance of the phenotype caused by the *lov-1* or *pkd-2* mutations for either or both of the 'response' and Lov defect. This is achieved by screening for males that cannot sire cross progeny with paralyzed hermaphrodite mating partners or by observing the behavior directly. The genes with mutations responsible for the increased penetrance that differ are identified and those that are not *lov-1* or *pkd-2* are selected. Mammalian, particularly human, homologs of the selected genes are identified, and tested to assess their role in PKD diseases, such as, for example, by screening PKD patients for alterations in the homologous (or orthologous) gene, analysis of mouse model knockout mutations, or other methods known to those of skill in the art.

Assays for identifying the role of PKD proteins in sensory function

As shown herein, *lov-1* and *pkd-2* are expressed in CEM neurons, indicating that they have activity in other sensory functions, such as finding a mating partner at a distance, *i.e.* sexual chemotaxis or kinesis, where the male randomly finds a hermaphrodite and then stays nearby. Hence sexual or chemoattraction assays can be used to study PKD function. To perform this assay, for example, put males that are

mutagenized or treated with a test compound on a surface containing at particular locations hermaphrodites and a control (*i.e*, males, or other hermaphrodites, or buffer), The proportion of fraction of males that choose the hemaphrodites compared to the control is scored. If the male is defective in this sensory function, it will not distinguish between males and hermaphrodites.

Other sensory functions can be assessed to identify the role, if any, of PKD genes in the functions.

Assays that use dominant negative forms of PKD in nematodes or in other cells to identify mutations and/or compounds that inhibit or otherwise alter PKD function

Transgenic nematodes that express a version of the LOV-1 or PK2D protein that inhibits the activity of LOV-1 and/or PKD-2 as assessed by manifestation of the altered LOV and/or response phenotypic behavior(s) are used in these assays.

As described above, a dominant negative mutation is a mutation that encodes a polypeptide that when expressed disrupts that activity of the protein encoded by the wild-type gene (see, Herskowitz (1987) *Nature 329*:219-222). A cloned gene is altered so that it encodes a mutant product that upon expression in an organism or cell containing the wild-type gene, expression of the wild-type product is inhibited or eliminated. As a result, the cell or organism is deficient in the product. The mutation is "dominant" because its phenotype is manifested in the presence of the wild-type gene, and it is "negative" in the sense that it inactivates the wild-type gene function. It is possible to do this because proteins have multiple functional sites. Hence an assay that identifies a dominant negative mutation can identify functional activities of a protein.

In this instance, the assays use transgenic nematodes that contain such a dominant negative *lov-1* or *pkd-2* transgene. In certain assays, the transgenic mutants are mutagenized, and mutants that lose a remaining activity are selected. The mutuations and genes responsible for

the lose are identifed. Corresponding mammalian, particularly human, genes, such as by searching databases for homlogs or by probing libraries with the nematode genes, are identified.

In the compounds screening assays that employe these transgenic nematodes, compounds that interfere with a remaining activity of the lov-1 or pkd-2 gene are identified. For example, as shown herein, plov-1.3 (plov-1.3 encodes a truncated protein lacking the polycystin block 2/channel domain) has a dominant negative effect in transgenic nematodes affecting only the Lov behavior, not Response. Compounds that rescue this dominant negative effect include those that interfere with the synthesis, binding or function of the amino-terminal region of the LOV-1 protein.

Since the dominant negative effect only affects the Lov response, a stable transgenic nematode strain that expresses a dominant negative of *lov-1*, can be used to screen for compounds and mutations that further affect Response well.

Assays based based on localization and trafficking of LOV-1 and/or PKD-2 within a cell or cells

To identify regulators and factors necessary for synthesis and transport of *LOV-1* and/or *PKD-2* proteins, strains in which LOV-1 and PKD-2 are expressed linked to a detectable label, such as a fluorescent protein, can be and have been produced. It has been shown that these proteins are expressed in the ciliated endings and in the baso-dendritic compartment of HOB, ray neurons or CEM neurons.

These strains, such as PS3149, described above, can be used to study the trafficking patterns of *LOV-1* and *PKD-2* and cellular location(s) of the proteins in the animal by looking for mutants thereof that have altered trafficking and/or altered localization of one or both of these proteins. The mutations can be mapped, genetically analyzed and the genes identified. Such genes could serve as therapeutic or diagnostic targets.

Assays for identification of transcriptional regulators of expression of *lov-1* and/or *pkd-2*

To identify transcriptional regulators of *lov-1* or *pkd-2*, a screen for loss or alteration of expression of either gene is provided. Transgenic nematodes with a reporter gene, such as a gene encoding a FP or lacZ or other detectable product, linked to the nucleic acid encoding *lov-1* or *pkd-2* is used. The animal is mutagenized or treated with a test compound and loss of expression or reduction in expression of either gene is assessed by detecting, such as by observing under a dissecting or compound microscope or other means, including whole animal sorting, the number of cells that express the detectable marker, such as a FP.

As a control, to avoid detection or identification of non-specific effects, an unrelated gene, such as *lin-3*, linked to a reporter, is expressed in other cells in these animals. Only mutatants that exhibit changes in expression of *lov-1* or *pkd-2*, but not expression of the other gene, are selected for identification and mapping of the mutation. If expression of the other gene is affected also, then mutation is likely affecting a general process and would not be of interest.

These assays will identify regulators of and factors that affect *lov-1* and *pkd-2* expression, which regulators and factors could serve as therapeutic or diagnostic targets, or which can aid in developing an understanding of the development and progression of PKD in mammals.

Visual screen based on clumping behavior

Wild type adult males isolated from hermaphrodites will clump together on a plate with a lawn of bacteria. In contrast, *lov-1* and *pkd-2* mutant males do not exhibit this clumping behavior. Rather, *lov-1* and *pkd-2* mutant males are randomly dispersed in the bacterial lawn. This assay may be used for a variety of purposes, including, but not limited to, the identification of compounds that inhibit wild type male clumping behavior, compounds that restore clumping behavior to *lov-1* or *pkd-2*

mutants, and the identification of genetic supressors of *lov-1* or *pkd-2* mutants.

Kits and diagnostic systems for performing the assays

Kits for use in screening for use in any of the assays are provided. The kits include transgenic or wild-type nematodes or both that express either wild-type or a mutant or a transgenic form of *lov-1* and/or *pkd-2*. The nematodes may be on plates, in wells or in any form suitable for the assays. Kits containing nucleic acid encoding either of the two genes, portions thereof or vectors or plasmids containg the nucleic acids or probes based upon these sequences or reporter gene constructss containing all or portions of either or both genes and a reporter molecule are also provided. The nucleic acids may be in solution, in lyophillized or other concentrated form, or may be bound to a suitable substrate. The kits can include additional reagents for performing the assays, such reagents include any for performing any of the steps of the methods. The kits include instructions for performing the assays.

The kits may also include suitable ancillary reagents, such as the appropriate buffers and reagents. The kits may also include suitable ancillary supplies, such as microtiter plates, vials, calibrator solutions, controls, wash solutions and solid-phase supports.

The kits are typically provided in packages customarily utilized in diagnostic assays. Such packages include glass and plastic, such as polyethylene, polypropylene and polycarbonate, bottles and vials, plastic and plastic-foil laminated envelopes and the like. The packages may also include containers appropriate for use in auto analyzers. The packages typically include instructions for performing the assays.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Identification of *C. elegans* orthologs of human polycystins

Mating behavior and mating efficiency assays. Males were generated by use of *him-5(e1490)* (high incidence of male) strains or by heatshock of L4 hermaphrodites (Brenner (1974) *Genetics* *77*:71-94). Mating efficiency (ME) tests were performed by pairing six tester L4 males with six paralyzed *unc-52* or four actively moving *dpy-17* or N2 L4 hermaphrodites. ME is the percentage of cross progeny to total progeny (Hodgkin (1983) *Genetics* *103*:43-64). Behavioral observations were done on a 0.5 cm diameter lawn of OP50 (Liu *et al.* *Neuron* *14*:79-89). Hermaphrodites (N2 or *unc-31(e169)*) were placed on a lawn with the tester male. Behavioral phenotypes were determined by keeping time with a stopwatch and manually recording the behavioral series. In one trial, a male is observed for a minimum of 10 vulva encounters or for 10 minutes, whichever comes first. A male who does not respond to hermaphrodite contact within 10 minutes is considered response defective. Response ability reflects the percentage of males successfully responding to hermaphrodite contact. An individual male's vulva location ability was calculated as: Number of positive vulva locations/Total number of vulva encounters. Ability can vary from 100% (always locate) to 0% (never locate). Vulva location efficiency indicates the average behavior of a genotypic population. Pairwise comparisons were made using Mann-Whitney nonparametric and two-sided t tests (Instat for MacIntosh).

Genetic screen for location of vulva (Lov mutants). PS1395 hermaphrodites of genotype *plg-1(e2001d); him-5(e1490)* were mutagenized with EMS (Brenner (1974) *Genetics* *77*:71-94). *plg-1(e2001d); him-5(e1490)* males deposit a gelatinous plug over the hermaphrodite vulva post coitum. A decrease in plugging efficiency might reflect a decrease in mating ability. An F1 clonal screen was performed by picking individual F1 progeny of mutagenized hermaphrodites to individual plates and directly observing F2 males for behavioral defects.

An F2 clonal screen was performed such that 10 F1 progeny per P0 hermaphrodite were picked to the same plate, 10 F2 hermaphrodites per F1 pool were picked to individual plates, and F3 males were observed for decreased plugging efficiency and/or location of vulva (Lov) defects. *lov-1(sy552); plg-1(e2001d); him-5* is a recessive mutation isolated in the F2 clonal screen. *lov-1(sy552)* males are response and Lov defective and also have a very low ME with *dpy-17* hermaphrodites (ME-Dpy).

Genetic mapping of *lov-1*. Chromosomal linkage of *lov-1(sy552)* was determined by scoring the loss of genetic markers relative to response, Lov, and ME-Dpy phenotypes, which revealed linkage between *dpy-10* and *sy552*. Further mapping was achieved via three factor crosses. From *sy552/unc-4(e120) let-25(mn25)* heterozygotes, Unc non-Let (Unc for uncoordinated, Let for lethal) recombinants were picked. As Unc males cannot mate, a test cross with *sy552* males and Unc hermaphrodites was performed to generate non-Unc *sy552/(sy552Δ)unc-25(mn25)* males. Males were scored for response, Lov, and ME-Dpy defects. 2/12 Unc non-Let recombinants segregate the *lov-1* mutant phenotype. These data placed *lov-1* between *unc-4* and *let-25*, closer to *unc-4*. Deficiency mapping indicated that *mnDf21* uncovers *sy552* whereas *eDf21* does not.

Transformation rescue of *lov-1(sy552)* mutants. Cosmids and plasmids (15-100 ng/μl) in the region from the right breakpoint of *eDf21* to the right breakpoint of *mnDf21* and PHA-1 (pBX, 100 ng/μl were injected into *lov-1(sy552); pha-1(e2123ts); htm-5(e1490)*. Stable lines were selected at either 19° or 25°C (Schnabel *et al.* (1990) *Science* *250*:686-688). Cosmid ZK945 rescued *sy552* response and vulva location defects in four of five stable lines. A 16.9 kb HindIII fragment of ZK945 cloned into pBS(SK+) (plov1.1) containing ORFs ZK945.10 and ZK945.9 rescued *sy552* behavioral defects in 4 of 6 stable lines. A 6.7 kb HindIII-BamHI fragment of ZK945 (plov-1::GFP1) containing ORF ZK945.10 did not rescue *sy552* defects. plov-1.3 creates a frameshift at

nucleotide 17724 in ZK945 inserting a BssHII GFP fragment from plasmid pPD95.02 out of frame into the StuI site of plov-1.1 plov-1.3 fails to rescue *sy552*.

PCR screen for genomic deletion of *lov-1*. Approximately 315,000 haploid genomes were screened using primers designed to delete the PKD/channel domain. Primer set 1 (SEQ ID Nos. 7 and 8, respectively), the outside primers were:

JC32 5'-CTCTATTTGTGGTTCGTTGGCG-3' and
JC36 5'-GGGAGTTTCCGTTTTCATGGGG-3'; and

internal nested primer set (SEQ ID Nos. 9 and 10, respectively) were:

JC33 5'-CTAGGACCGATGCAACAGCGAG-3' and
JC35 5'-AACGCTGATTGGTTCAAGTGTG-3')

are approximately 2.5 and 2.4 kb apart, respectively. One deletion allele, *lov-1(sy582Δ)* was isolated. DNA sequence analysis indicated a deletion of nucleotides 16972 to 18027 of ZK945.

DNA-sequence analysis. RT-PCR from *him-5(e1490)* RNA using a combination of *lov-1* primers generated overlapping cDNA clones bridging the junction between ZK945.10 and ZK945.9. Genefinder had predicted boundaries of the last exon of ZK945.10 (from position 25742 to 25174 of ZK945) and first exon of ZK945.9 (24923 to 24444). DNA sequence analysis of RT-PCR generated cDNA clones revealed three exons in the junction: one from 25742 to 25195, a second from 25151 to 25071, and a third initiating a position 25021, corresponding to exons I, J, and K, in Fig. 2b, respectively.

PCR screen for genomic deletion of *pkd-2*

For pkd-2 the used primers (SEQ ID Nos. 11-14, respectively) were as follows:

Outside primers

LOV2.9 (Y73F8A nt 8546-8569) 5' CCCCTCGTTTGACCATTCTATGG 3'
LOV2.10 (Y73F8A nt 8438-8457) 5' ACGTGATCCTCTGTCGATCCAG 3'

Nested Primers

LOV2.9A(Y73F8A nt 5599-5615) 5′ AGATCAAGCTGACTGCCCGTTC 3′
LOV2.10A(Y73F8A nt 5609-5631) 5′GATCCAGCGATTAGCCTTTAA CG3′/
One deletion allele, *pkd-2(sy606)* was isolated, which has a 2397 bp deletion from nucleotides 8338 to 5942 of Y73F8A (GenBank Accession No. AL132862; corresponding to nucleotides 6734 to 4338 of SEQ ID NO. 5). The deletion starts in intron 3 and ends in intron 5, removing exons 4 and 5 (including the partial transmembrane spanning domain S1 and the polycystin motif) with the new splice in a different reading frame resulting in a stop codon (TGA) at 5736, produced a knockout mutation. The resulting phenotype was the same as that resulting from a knockout of *lov-1*, thereby demonstrating that the two proteins are part of the same pathway that results in the observed phenotype.

EXAMPLE 2

Expression analyses of LOV-1 and PKD-2

Methods

GFP (see, Chalfie *et al.* (1994) *Science 263*:802-805) expression was used a marker for *lov-1* and *pkd-2* gene expression (see Figs. 3a and 4A) plov-1::GFP1 was constructed by cloning a 6.7 kb *Hind*III-*Bam*HI fragment of plov-1.1 into the vector pPD95.81, plov-1::GFP2 by cloning a *Hind*III-*Hpa*I fragment. plov-1::GFP3 and plov-1::GFP4 are *Sac*I and *Hind*III-*Hpa*I (Klenow filled-in and religated) deletions of plov-1::GFP1, respectively. plov-1::GFP5 was constructed by cloning a 15.4 kb *Hind*III-*Afe*I fragment of plov-1.1 into the *Hind*III-*Sma*I site of pPD95.79. ppkd-2.1, ppkd-2::gfp1 and ppkd-2::gfp2 were constructed by cloning PCR-amplified 8.9 kb, 2.0 kb and 5.9 kb fragments into the vectors pPD95.97, pPD95.75 and pPD95.77, respectively. Transgenic animals were observed by fluorescence microscopy Cells were identified by comparing Nomarski and fluorescent or confocal images of the same animals to determine cell-body position (Sulston *et al.* (1980) *Dev. Biol. 78*:542-576). HOB assignment was confirmed by laser ablation of precursor cells.

lov-1 expression

lov-1::GFP1 is specifically expressed in male-sensory neurons, including four putative chemosensory CEM cephalic neurons, the hook neuron HOB (Fig. 4a), and the sensory ray neurons (Fig. 4b). *lov-1::GFP1* expression was first observed in a few cells during late L4 lethargus (data not shown) while strong expression peaks in the adult male. In neuronal cell bodies, GFP expression is cytoplasmic (non-nuclear) and punctate (Fig. 4a and Fig. 4b). *lov-1::GFP1* is localized at high levels in the cell body and ciliated endings of CEM (Fig. 4c), HOB, and ray neurons (Fig. 4b) but is not observed in axons. Localization of *lov-1::GFP1* to sensory endings is consistent with plasma membrane localization and strengthens the argument that *lov-1* mediates sensory perception required for mating behaviors. The temporal and spatial regulation of *lov-1* is concordant with its role in adult male mating behavior. Rays mediate response to contact with a hermaphrodite (Liu *et al. Neuron 14*:79-89), the hook mediates vulva location (Liu *et al. Neuron 14*:79-89), and the CEMs are postulated to play a role in chemosensation (Ward *et al.* (1975) *J. Comp. Neurol. 160*:313-337).

lov-1::GFP1 expression was unaltered in *lov-1(sy552)* mutants. Expression of this fusion gene did not rescue *lov-1(sy552)* defects (Fig. 2a) and is therefore not functional. Sensory neurons and structures are normal in *lov-1(sy552)* mutants as determined by *osm-6::gfp* expression, dye filling of sensory neurons, Nomarski observation, and SEM imaging (data not shown). The defects of *lov-1(sy552)* mutants therefore cannot be attributed to abnormal development or differentiation of the response and vulva location neurons. This indicats hat *lov-1(sy552)* defects are due to defects in the function of the cells required for response and vulva location.

The Lov defect of mutations in *lov-1* is not identical to ablation of HOB, the chemosensory neuron in which *lov-1* expressed. The *lov-1* mutant and HOB-ablated males pass the vulva (Fig. 1). The *lov-1* males,

however, are capable of precisely locating the vulva, whereas HOB-ablated males resort to slow search. Therefore, the HOB neuron of *lov-1* functions, albeit in an attenuated capacity. If *lov-1(sy552)* and *lov-1(sy582Δ)* are loss of function alleles as the data suggests, then additional components are involved in Lov sensation.

Chemosensation and mechanosensation are likely involved in Lov *C elegans* sensory neurons can be polymodal: for example, by ultrastructural assignment, the ASH neuron appears to be chemosensory yet functions in both mechanosensory (nose touch) and chemosensory (osmotic avoidance) modalities (Kaplan *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A. 90*:2227-2231). HOB might similarly be a polymodal sensory neuron. Ablation of either HOA or HOB produces identical phenotypes (Liu *et al. Neuron 14*:79-89) and HOA and HOB form multiple chemical synapses and electrical junctions (Sulston *et al.* (1980) *Dev. Biol. 78*:542-576), indicating extensive cross talk between the two hook sensory neurons. Since LOV-1 has an extensive extracellular mucin-like domain that could be involved in cell-cell or cell-matrix interaction, binding of vulva cell ligand(s) might potentially gate the LOV-1 polycystin-related channel. Another possibility is that LOV-1 could physically link the HOB sensory endings to the scherotized hook structure and couple hook deflection by the hermaphrodite vulva to intracellular voltage-activated signaling similar to hair cell mechanosensation (Hudspeth (1989) *Nature 341*:397-404) or touch response in *C. elegans* (Driscoll *et al.* in *C. elegans II* (ed. Riddle, D.I., Blumenthal, T., Meyer, B.J., and Priess, J.R.) 645-677 (Cold Spring Harbor Laboratory Press, New York, 1997).

pkd-2 expression

As shown herein, *C. elegans* genome contains a human PKD-2 homlog. PKD-2 possesses six membrane-spanning domains, a positively charged foruth membrane-spanning segment, a pore region, and the coiled coil domain of all polysystins. PKD-2 is localized to the same male-specific sensory neuorons as LOV-1 (see, Fig. 3 and Fig. 4).

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

SEQUENCE LISTING SUMMARY

SEQ ID No. 1 cDNA encoding human PKD1

SEQ ID No. 2 encoded human PKD1 protein

SEQ ID No. 3 sequence of a gene encoding nematode LOV-1 protein

SEQ ID No. 4 encoded nematode *LOV-1* protein

SEQ ID No. 5 sequence of a gene encoding a nematode *PKD-2* protein

SEQ ID No. 6 encoded nematode *PKD-2* protein

SEQ ID No. 7 primer for *lov-1* deletion mutant construction

SEQ ID No 8 primer for *lov-1* deletion mutant construction

SEQ ID No. 9 internal primer for *lov-1* deletion mutant construction

SEQ ID No. 10 internal primer for *lov-1* deletion mutant construction

SEQ ID No. 11 primer for *pk2-1* deletion mutant construction

SEQ ID No. 12 primer for *pk2-1* deletion mutant construction

SEQ ID No. 13 internal primer for *pk2-1* deletion mutant construction

SEQ ID No. 14 internal primer for *pk2-1* deletion mutant construction

SEQ ID No. 15 sets forth the a *LOV-1* mutant protein from *sy582*

SEQ ID No. 16 sets a *PKD-2* mutant protein from *sy606*

CLAIMS:

1. An isolated nucleic acid molecule, comprising:

a) a sequence of nucleotides that encodes the sequence of amino acids encoded by one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No. 3; or

b) the sequence of nucleotides set forth as one or more of the exons that are the complement of the sequence of nucleotides set forth in SEQ ID No. 3;

c) a sequence of nucleotides that hybridizes along its full length to the full length of at least one of the exons set forth in SEQ ID No. 3 under conditions of at least moderate stringency, and that is present it the genome of a nematode; or

d) a sequence of nucleotides degenerate with the sequence of nucleotides of c).

2. An isolated nucleic acid molecule, comprising:

a) a sequence of nucleotides that encodes the sequence of amino acids encoded by one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No.5; or

b) the sequence of nucleotides set forth as one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No. in SEQ ID No. 5;

c) a sequence of nucleotides that hybridizes along its full length to the full length of at least one of the exons of SEQ ID No. 5 under conditions of at least moderate stringency, and that is present in the genome of a nematode; or

d) a sequence of nucleotides degenerate with the sequence of nucleotides of c).

3. An isolated nucleic acid molecule of claim 1, that encodes LOV-1 protein from a nematode.

4. An isolated nucleic acid molecule of claim 2, that encodes a PKD-2 protein from a nematode.

5. The isolated molecule of claim 1 that comprises a sequence of nucleotides that encodes the amino acids set forth in SEQ ID No. 4.

6. The isolated molecule of claim 2 that comprises a sequence of nucleotides that encodes the amino acids set forth in SEQ ID No. 6.

7. The isolated nucleic acid molecule of claim 1, wherein the nematode is *Caenorhabditis elegans*.

8. The isolated nucleic acid molecule of claim 2, wherein the nematode is *Caenorhabditis elegans*.

9. An isolated gene, comprising the nucleic acid molecule of claim 1.

10. The gene of claim 9, wherein the gene comprises transcriptional control sequences that are homologous to the encoded gene.

11. The gene of claim 9, wherein the gene comprises transcriptional control sequences that are heterologous to the encoded gene.

12. An isolated gene, comprising the nucleic acid molecule of claim 2.

13. The gene of claim 12, wherein the gene comprises transcriptional control sequences that are homologous to the encoded gene.

14. The gene of claim 12, wherein the gene comprises transcriptional control sequences that are heterologous to the encoded gene.

15. An isolated nucleic acid molecule that encodes a mutant of the protein encoded by the nucleic acid molecule of claim 3.

16. The nucleic acid molecule of claim 15, wherein the mutant is a deletion mutant, insertional mutant or comprises a point mutation.

17. The nucleic acid molecule of claim 15, wherein the encoded protein is inactive.

18. An isolated nucleic acid molecule that encodes a mutant of the protein encoded by the nucleic acid molecule of claim 4.

19. The nucleic acid molecule of claim 18, wherein the mutant is a deletion mutant, insertional mutant or comprises a point mutation.

17. The nucleic acid molecule of claim 18, wherein the encoded protein is inactive.

18. A construct, comprising a nucleic acid molecule of claim 1 operatively linked to a reporter gene.

19. The construct of claim 18, wherein the reporter gene encodes a fluorescent protein.

20. A construct, comprising a nucleic acid molecule of claim 2 operatively linked to a reporter gene.

21. The construct of claim 20, wherein the reporter gene encodes a fluorescent protein.

22. A plasmid, comprising a nucleic acid molecule of claim 1.

23. The plasmid of claim 22 that is an expression vector.

24. A transgenic nematode, comprising the vector of claim 23.

25. The transgenic nematode of claim 24, wherein in the vector is maintained extrachromsomally.

26. The transgenic nematode of claim 24, wherein in the vector or a gene-encoding portion is integrated into the *C. elegans* genome.

27. The transgenic nematode of claim 24, wherein the vector further comprises nucleic acid encoding a reporter gene operatively linked to the nucleic acid molecule.

28. The transgenic nematode of claim 24, wherein the nucleic acid molecule encodes a mutant protein.

29. The transgenic nematode of claim 27, wherein the nucleic acid molecule encodes a mutant protein.

30. A plasmid, comprising a nucleic acid molecule of claim 2.

31. The plasmid of claim 30 that is an expression vector.

32. A transgenic nematode, comprising the vector of claim 31.

33. The transgenic nematode of claim 32, wherein in the vector is maintained extrachromosomally.

34. The transgenic nematode of claim 32, wherein in the vector or the gene-encoding portion is integrated into the *C. elegans* genome.

35. The transgenic nematode of claim 32, wherein the vector further comprises nucleic acid encoding a reporter gene operatively linked to the nucleic acid molecule.

36. The transgenic nematode of claim 32, wherein the nucleic acid molecule encodes a mutant protein.

37. The transgenic nematode of claim 35, wherein the nucleic acid molecule encodes a mutant protein.

38. An isolated nucleic acid molecule, comprising a sequence of nucleotides encoding a mutant LOV-1 protein, wherein a nematode that expresses such defect exhibits one or both of an altered location of vulva (Lov) and response phenotype, and the LOV-1 protein is encoded by the nucleic acid molecule of claim 1.

39. A transgenic nematode, comprising the nucleic acid molecule of claim 38.

40. An isolated nucleic acid molecule, comprising a sequence of nucleotides encoding a mutant PKD-2 protein, wherein a nematode that expresses such defect exhibits one or both of an altered Lov and response phenotype, and the PKD-2 protein is encoded by the nucleic acid molecule of claim 2.

41. A trangenic nematode, comprising the nucleic acid molecule of claim 40.

42. An isolated polypeptide encoded by the nucleic acid molecule of claim 1.

43. The polypeptide of claim 42 that comprises the sequence of amino acids set forth in SEQ ID No. 4.

44. An isolated polypeptide encoded by the nucleic acid molecule of claim 2.

45. The polypeptide of claim 44 that comprises the sequence of amino acids set forth in SEQ ID No. 6.

46. An isolated nucleic acid molecule of claim 19, comprising a sequence of nucleotides that encodes the sequence of amino acids set forth in SEQ ID No. 15.

47. An isolated complex comprising a nematode PKD-2 protein and a nematode LOV-1 protein in operative linkage.

48. A method, comprising:

introducing a mutation into the *lov-1* and/or *pkd-2* gene of a nematode, and

selecting nematodes that exhibit altered mating behavior, wherein the altered behavior includes a change in the ability to locate the vulva (Lov) of a hermaphrodite or a change in the response of the male to contact with the hermaphrodite (Response).

49. The method of claim 48, wherein the altered behavior is a change in the response of the male to contact with the hermaphrodite.

50. The method of claim 48, wherein the mutation is in the *lov-1* gene.

51. The method of claim 48, wherein the mutation is in the *pkd-2* gene.

52. The method of claim 48, wherein the nematode is a species of *Caenorhabditis*.

53. A method, comprising:

treating nematodes with a test compound or with a mutagenizing agent or treatment; and

selecting from among the nematodes or offspring thereof, nematodes that exhibit altered mating behavior compared to prior to the treatment; where the altered behavior includes one or both of location of vulva (Lov) or response of the male to contact with the hermaphrodite (Response).

54. The method of claim 53, wherein prior to treatment the nematodes had exhibited normal mating behavior.

55. The method of claim 53, wherein prior to treatment the nematodes had exhibited defects in mating behavior, wherein the defects were manifested as a defect in one or both of Lov and Response, and the alteration comprises a partial restoration or complete restoration of one or both of Lov and Response behaviors.

56. A method for identifying compounds, comprising:

contacting nematodes with a test compound;

selecting test compounds that result in altered mating behavior, wherein:

the altered mating behavior comprises alteration in the behavior involving location of vulva and/or response to contact with the hermaphrodite; and

the selected test compounds are candidates for treatment of polycystic kidney diseases of mammals.

57. The method of claim 56, wherein prior to treatment the nematodes had exhibited normal mating behavior.

58. The method of claim 56, wherein prior to treatment the nematodes had exhibited defects in mating behavior, wherein the defects were manifested as a defect in one or both of Lov and Response, and the alteration comprises a partial restoration or complete restoration of one or both of Lov and Response behaviors.

59. The method of claim 56, wherein the selected compounds are candidate therapeutic agents for treatment of autosomal dominant polycystic kidney disease (ADPKD) or other diseases involving PKD1 or PKD2.

60. The method of claim 59, wherein prior to treatment the nematodes had defects in mating behavior, and the candidate compounds restore or partially restore either or both Lov and Response.

61. A method for identifying genes that are part of the disease pathway of autosomal dominant polycystic kidney disease (ADPKD), comprising:

mutagenizing nematodes that exhibit normal mating behavior; and

identifying and selecting nematodes or the male offspring thereof that exhibit altered mating behavior, wherein the altered mating behavior comprises alteration in the behavior involving location of vulva (LOV) and/or response to contact with the hermaphrodite (Response), thereby identifying nematodes that contain defects in genes in the pathway that comprises the *lov-1* and/or *pkd-2* gene(s).

62. The method of claim 61, further comprising, mapping the mutation(s) in selected nematodes that results in the altered behavior.

63. The method of claim 62, further comprising, identifying mammalian homologs or orthologs of the nematode genes to which the mutation is mapped.

64. A method for identifying compounds that are candidate therapeutic agents for treatment of autosomal dominant polycystic kidney disease (ADPKD), comprising:

treating male nematodes that can sire cross-progeny with moving partners with a test compound; and

selecting compounds that result in males that sire fewer cross progeny or cannot sire cross-progeny with moving partners, wherein the selected compounds are candidate therapeutic agents for treatment of ADPKD or diseases involving PKD1 or PKD2.

65. A method for identifying genes that are part of the disease pathway of autosomal dominant polycystic kidney disease (ADPKD), comprising:

mutagenizing males nematodes that can sire cross-progeny with moving partners with a test compound;

selecting males or the offspring thereof that sire fewer cross-progeny with moving partners; and

identifying the mutant nematode genes.

66. A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

mutagenizing nematodes that exhibit altered mating behaviors because of a mutation in the *lov-1* or *pkd-2* gene;

selecting nematodes or the offspring thereof that exhibit a restoration of the behavior associated with the wild-type gene; and

identifying a second gene other than *lov-1* or *pkd-2* or a factor that results in restoration of the behavior, wherein restoration of the behavior is a partial or complete restoration compared to prior to mutagenesis.

67. The method of 66, further comprising:

identifying a mammalian gene that is orthologous to the second gene.

68. A method for screening compounds to identify candidates for treatment of polycystic kidney diseases, comprising:

contacting nematodes that exhibit altered mating behaviors because of a mutation in the *lov-1* or *pkd-2* gene with a test compound; and

selecting compounds that result in restoration of the behavior, wherein restoration of the behavior is a partial or complete restoration compared to prior to contacting.

69. A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

mutagenizing nematodes that exhibit altered mating behaviors because of a mutation in the *lov-1* or *pkd-2* gene;

selecting nematodes or offspring thereof that cannot sire cross progeny or sire fewer cross progeny with paralyzed hermaphrodite mating partners; and

identifying a gene responsible for the inability to sire cross progeny with paralyzed hermaphrodite mating partners.

70. The method of claim 69, further comprising identifying mammalian homologs of the gene responsible for the inability to sire cross progeny with paralyzed hermaphrodite mating partners.

71. A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

mutagenizing transgenic nematodes that contain a dominant negative *lov-1* or *pkd-2* transgene;

selecting nematodes or offspring thereof that exhibit a further loss in function of the *lov-1* or *pkd-2* transgene by observing mating behaviors; and

identifying the mutations and genes responsible for the loss.

72. The method of claim 71, further comprising identifying homologous mammalian genes.

73. A method for identifying regulators and factors necessary for synthesis and transport of *LOV-1* or *PKD-2* protein;

preparing a transgenic nematode that expresses a detectable marker linked to *LOV-1* or *PKD-2* protein;

mutagenizing the nematode;

selecting nematodes or offspring thereof that have altered patterns of expression of *LOV-1* or *PKD-2*; and

identifying the gene responsible for the alteration.

74. A method for identifying transcriptional regulators of *lov-1* or *pkd-2*; comprising:

preparing a transgenic nematode that expresses a detectable marker linked to *LOV-1* or *PKD-2* protein;

mutagenizing the nematode;

selecting nematodes or offspring thereof that altered levels of expression of the protein.

75. A method, comprising:

treating nematodes with a test compound or mutagenizing them;

selecting nematodes or the offspring thereof that exhibit altered clumping behavior when seeded on a lawn of bacteria, wherein:

an alteration in the behavior is indicative of change in the genotype of the *lov-1* or *pkd-2* locus;

the wild-type males exhibit clumping behavior, and a males with a mutation in either locus that alters activity of either the LOV-1 or PKD-2 protein results in males that are randomly dispersed in the bacterial lawn.

76. The method of claim 75, wherein:

the nematodes are mutant nematodes that are randomly dispersed in the bacterial lawn and are treated with a test compound; and the method further comprises:

identifying compounds that restore or partially restore clumping behavior.

77. The method of claim 76, wherein the mutant nematodes comprise males that are *lov-1* mutants.

78. The method of claim 76, wherein the mutant nematodes comprise males that are *pkd-2* mutants.

79. The method of claim 75, wherein:

the nematodes are mutant nematodes that are randomly dispersed in the bacterial lawn and then mutagenized; and the method further comprises:

selecting males or the offspring thereof that exhibit a partial or complete restoration of the behavior;

analyzing the mutations; and

identifying the genes or mutations responsible for the restoration.

80. The method of claim 76, wherein the genes or mutations are genetic supressors of *lov-1* or *pkd-2* mutants.

81. The method of claim 76, wherein the mutant nematodes comprise males that are *lov-1* mutants.

82. The method of claim 76, wherein the mutant nematodes comprise males that are *pkd-2* mutants.

83. The method of claim 75, wherein:

the nematodes are wild-type nematodes that are clumped in the bacterial lawn and are treated with a test compound; and the method further comprises:

identifying compounds that destroy the clumping behavior.

84. The method of claim 75, wherein:

the nematodes are wild-type nematodes that are clumped in the bacterial lawn and then mutagenized; and the method further comprises:

selecting males or the offspring there of that are randomly dispersed on the bacterial lawn;

analyzing mutations responsible for the altered behavior; and

identifying the mutant genes.

85. A mutant strain of nematode that comprises a mutation in the *lov-1* or *pkd-2* gene, whereby the resulting nematode exhibits altered mating behavior compared to the wild-type, wherein the alteration is manifested as either or both a defect in behavior involving location of vulva (LOV) and response to contact with the hermaphrodite (Response).

86. The mutant strain of claim 85, wherein the mutation is in the *lov-1* gene, wherein the wild-type *lov-1* gene comprises:

a) a sequence of nucleotides that encodes the sequence of amino acids encoded by one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No. 3; or

b) the sequence of nucleotides set forth as one or more of the exons that are the complement of the sequence of nucleotides set forth in SEQ ID No. 3;

c) a sequence of nucleotides that hybridizes along its full length to the full length of at least one of the exons set forth in SEQ ID No. 3 under conditions of at least moderate stringency, and that is present it the genome of a nematode; or

d) a sequence of nucleotides degenerate with the sequence of nucleotides of c).

87. The mutant strain of claim 85, wherein the mutation is in the *pkd-2* gene, wherein the wild-type *pkd-2* gene comprises:

a) a sequence of nucleotides that encodes the sequence of amino acids encoded by one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No.5; or

b) the sequence of nucleotides set forth as one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No. in SEQ ID No. 5;

c) a sequence of nucleotides that hybridizes along its full length to the full length of at least one of the exons of SEQ ID No. 5 under conditions of at least moderate stringency, and that is present in the genome of a nematode; or

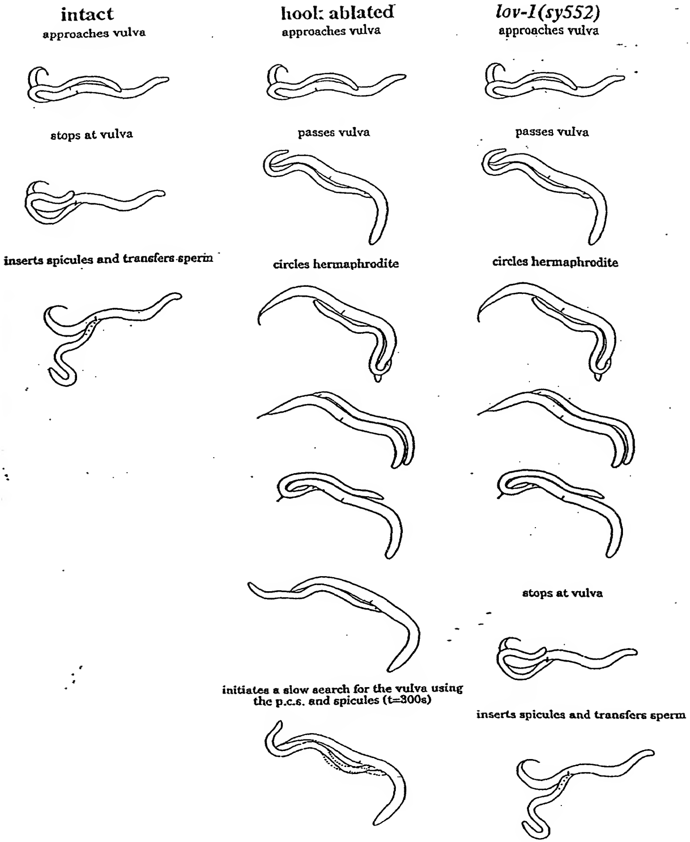
d) a sequence of nucleotides degenerate with the sequence of nucleotides of c).

88. The method of claim 65, further comprising identifying mammalian homologs of the genes that comprise the mutant nematode genes.

ABSTRACT

Nematodes, such as *Caenorhabditis elegans*, that express mutant and wild-type orthologs of human genes involved in polycystic kidney diseases (PKDs), are used to study the functions of the proteins encoded by the genes, to screen for other genes involved in the diseases, to identify mutations involved in the diseases, and to screen for drugs that affect PKD. Behaviors controlled by the action of the genes or gene products are identified and used in the assays. Hence an animal model is provided that permits study of the etiology of polycystic kidney disease and provides a tool to identify the genes involved in the disease pathway, and to identify compounds that may be used to treat or alter the disease progression, lessen its severity or ameliorate symptoms. The nematode genes that encode protein products, mutants of the genes, vectors contain the genes and mutant genes and nematode strains that contain the vectors are also provided.

FIG. 1



intact
approaches vulva
stops at vulva
inserts spicules and transfers sperm
hook ablated
approaches vulva
passes vulva
circles hermaphrodite
initiates a slow search for the vulva using the p.c.s. and spicules (t=300s)
lov-1(sy552)
approaches vulva
passes vulva
circles hermaphrodite
stops at vulva
inserts spicules and transfers sperm

Figure 2

A. *lov-1(sy552)* rescue data

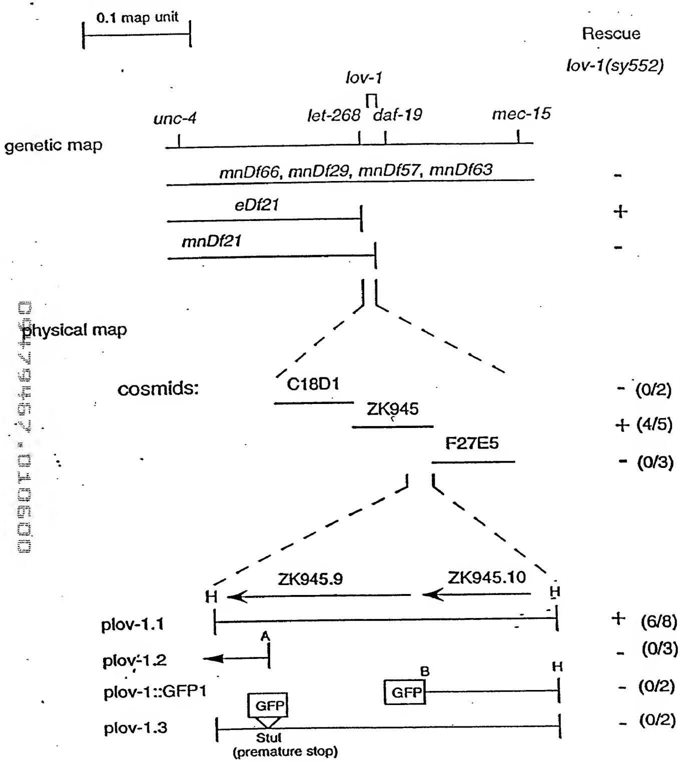
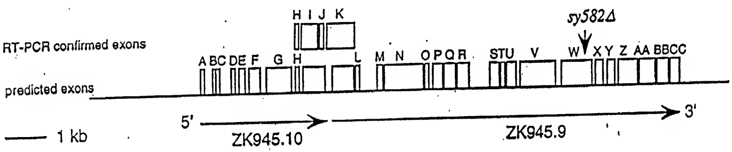
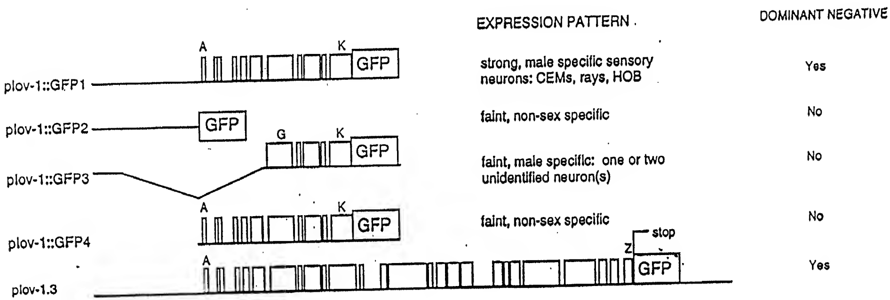


FIGURE 2B

B. *lov-1* gene structure: 16.7 kb rescuing clone



C. Schematic of GFP fusion constructs and expression data



09479467 .010600

D. LOV-1 structural features and sequence homologies

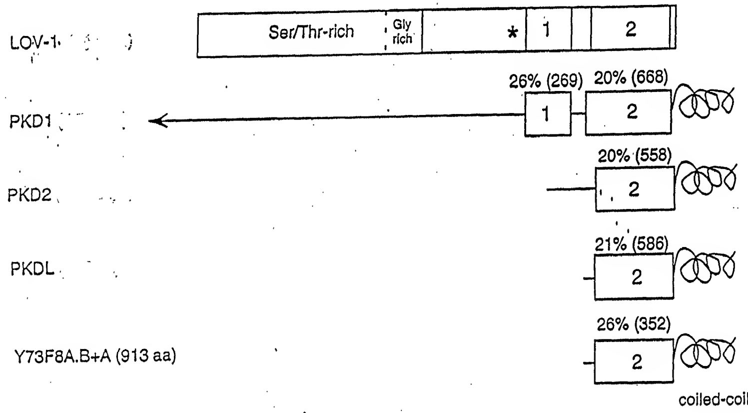


FIG.3

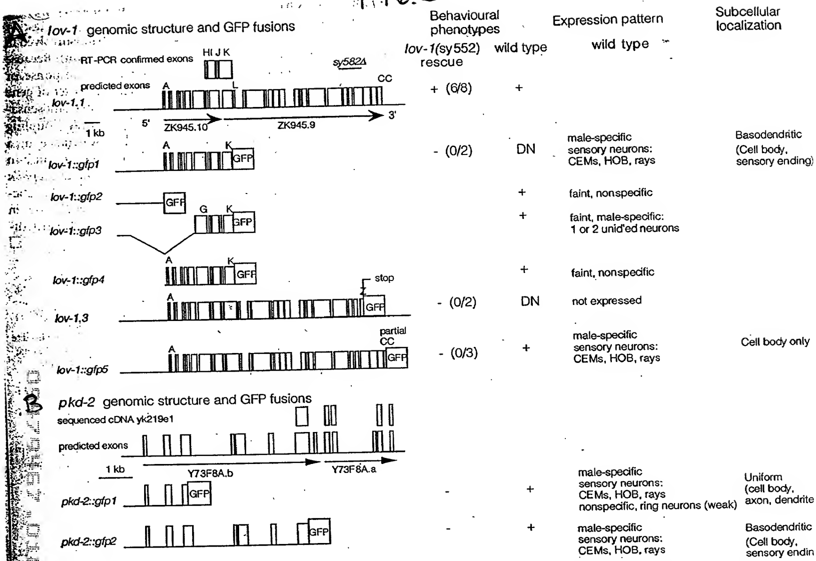


Figure 3 *lov-1* and *pkd-2* genomic structures, constructs, rescue data and expression patterns. The line above the *lov-1* gene indicates the 1,055-bp deletion in *lov-1(sy582Δ)*. Numbers in parentheses indicate the ratio of rescuing stable lines to the numbe stable lines examined. DN, dominant negative.

FIG 4

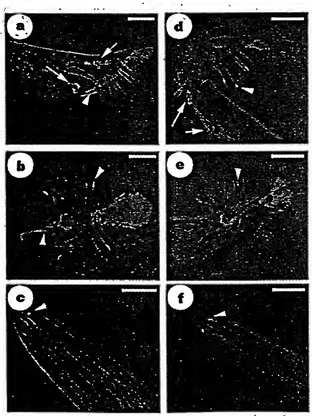


Figure 4 LOV-1::GFP1 and PKD-2::GFP2 are colocalized to adult male sens cell bodies and dendrites. The spicules, hook structure and posteriormost fa autofluoresce. Arrows, neuronal cell bodies; arrowheads, dendrites or ciliate Images (merged DIC and fluorescence) were obtained using confocal micros **a–c**, *lov-1::gfp1*. **a**, HOB and ray cell bodies (arrows), HOB dendritic process (a **b**, HOB and ray process 5 (arrowheads). **c**, Ciliated endings in nose tip from m cephalic CEM neurons (cell bodies not shown). **d–f**, *pkd-1::gfp2*. **d**, Ray cel (arrow) and ray process 2 (arrowhead). **e**, Ray process 5 (arrowhead). **f**, Mal cephalic CEM ciliated endings (arrow). Scale bar, 20 μm.

SEQUENCE LISTING

<110> Sternberg, Paul W.
Barr, Maureen M.

<120> POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON

<130> 18021-2901

<140> Unassigned
<141> 2000-01-06

<150> 60/115,127

<151> 1999-01-06

<160> 16

<170> PatentIn Ver. 2.0

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ctg tgg ctc ggg gcg ctg gcg ggg ggg ccc ggg cgc ggc tgc ggg ccc     96
Leu Trp Leu Gly Ala Leu Ala Gly Gly Pro Gly Arg Gly Cys Gly Pro
             20                  25                  30

tgc gag ccc ccc tgc ctc tgc ggg cca gcg ccc ggc gcc gcc tgc cgc    144
Cys Glu Pro Pro Cys Leu Cys Gly Pro Ala Pro Gly Ala Ala Cys Arg
         35                  40                  45

gtc aac tgc tcg ggc cgc ggg ctg cgg acg ctc ggt ccc gcg ctg cgc    192
Val Asn Cys Ser Gly Arg Gly Leu Arg Thr Leu Gly Pro Ala Leu Arg
     50                  55                  60

atc ccc gcg gac gcc aca gag cta gac gtc tcc cac aac ctg ctc cgg    240
Ile Pro Ala Asp Ala Thr Glu Leu Asp Val Ser His Asn Leu Leu Arg
 65                  70                  75                  80

gcg ctg gac gtt ggg ctc ctg gcg aac ctc tcg gcg ctg gca gag ctg    288
Ala Leu Asp Val Gly Leu Leu Ala Asn Leu Ser Ala Leu Ala Glu Leu
                 85                  90                  95

gat ata agc aac aac aag att tct acg tta gaa gaa gga ata ttt gct    336
Asp Ile Ser Asn Asn Lys Ile Ser Thr Leu Glu Glu Gly Ile Phe Ala
            100                 105                 110

aat tta ttt aat tta agt gaa ata aac ctg agt ggg aac ccg ttt gag    384
Asn Leu Phe Asn Leu Ser Glu Ile Asn Leu Ser Gly Asn Pro Phe Glu
        115                 120                 125

tgt gac tgt ggc ctg gcg tgg ctg ccg caa tgg gcg gag gag cag cag    432
Cys Asp Cys Gly Leu Ala Trp Leu Pro Gln Trp Ala Glu Glu Gln Gln
    130                 135                 140
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145                 150                 155                 160

ctg gct ggc cag cct ctg ctt ggc atc ccc ttg ctg gac agt ggc tgt     528
Leu Ala Gly Gln Pro Leu Leu Gly Ile Pro Leu Leu Asp Ser Gly Cys
                165                 170                 175

ggt gag gag tat gtc gcc tgc ctc cct gac aac agc tca ggc acc gtg     576
Gly Glu Glu Tyr Val Ala Cys Leu Pro Asp Asn Ser Ser Gly Thr Val
            180                 185                 190

gca gca gtg tcc ttt tca gct gcc cac gaa ggc ctg ctt cag cca gag     624
Ala Ala Val Ser Phe Ser Ala Ala His Glu Gly Leu Leu Gln Pro Glu
        195                 200                 205

gcc tgc agc gcc ttc tgc ttc tcc acc ggc cag ggc ctc gca gcc ctc     672
Ala Cys Ser Ala Phe Cys Phe Ser Thr Gly Gln Gly Leu Ala Ala Leu
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tcg gag cag ggc tgg tgc ctg tgt ggg gcg gcc cag ccc tcc agt gcc     720
Ser Glu Gln Gly Trp Cys Leu Cys Gly Ala Ala Gln Pro Ser Ser Ala
225                 230                 235                 240

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Ser Phe Ala Cys Leu Ser Leu Cys Ser Gly Pro Pro Ala Pro Pro Ala
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ccc acc tgt agg ggc ccc acc ctc ctc cag cac gtc ttc cct gcc tcc     816
Pro Thr Cys Arg Gly Pro Thr Leu Leu Gln His Val Phe Pro Ala Ser
            260                 265                 270

cca ggg gcc acc ctg gtg ggg ccc cac gga cct ctg gcc tct ggc cag     864
Pro Gly Ala Thr Leu Val Gly Pro His Gly Pro Leu Ala Ser Gly Gln
        275                 280                 285

cta gca gcc ttc cac atc gct gcc ccg ctc cct gtc act gac aca cgc     912
Leu Ala Ala Phe His Ile Ala Ala Pro Leu Pro Val Thr Asp Thr Arg
    290                 295                 300

tgg gac ttc gga gac ggc tcc gcc gag gtg gat gcc gct ggg ccg gct     960
Trp Asp Phe Gly Asp Gly Ser Ala Glu Val Asp Ala Ala Gly Pro Ala
305                 310                 315                 320

gcc tcg cat cgc tat gtg ctg cct ggg cgc tat cac gtg acg gcc gtg     1008
Ala Ser His Arg Tyr Val Leu Pro Gly Arg Tyr His Val Thr Ala Val
                325                 330                 335

ctg gcc ctg ggg gcc ggc tca gcc ctg ctg ggg aca gac gtg cag gtg     1056
Leu Ala Leu Gly Ala Gly Ser Ala Leu Leu Gly Thr Asp Val Gln Val
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gaa gcg gca cct gcc gcc ctg gag ctc gtg tgc ccg tcc tcg gtg cag     1104
Glu Ala Ala Pro Ala Ala Leu Glu Leu Val Cys Pro Ser Ser Val Gln
        355                 360                 365

agt gac gag agc ctc gac ctc agc atc cag aac cgc ggt ggt tca ggc     1152
Ser Asp Glu Ser Leu Asp Leu Ser Ile Gln Asn Arg Gly Gly Ser Gly
    370                 375                 380

ctg gag gcc gcc tac agc atc gtg gcc ctg ggc gag gag ccg gcc cga     1200
Leu Glu Ala Ala Tyr Ser Ile Val Ala Leu Gly Glu Glu Pro Ala Arg
385                 390                 395                 400

gcg gtg cac ccg ctc tgc ccc tcg gac acg gag atc ttc cct ggc aac     1248
Ala Val His Pro Leu Cys Pro Ser Asp Thr Glu Ile Phe Pro Gly Asn
                405                 410                 415
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ggg cac tgc tac cgc ctg gtg gtg gag aag gcg gcc tgg ctg cag gcg    1296
Gly His Cys Tyr Arg Leu Val Val Glu Lys Ala Ala Trp Leu Gln Ala
            420                 425                 430

cag gag cag tgt cag gcc tgg gcc ggg gcc gcc ctg gca atg gtg gac    1344
Gln Glu Gln Cys Gln Ala Trp Ala Gly Ala Ala Leu Ala Met Val Asp
        435                 440                 445

agt ccc gcc gtg cag cgc ttc ctg gtc tcc cgg gtc acc agg agc cta    1392
Ser Pro Ala Val Gln Arg Phe Leu Val Ser Arg Val Thr Arg Ser Leu
    450                 455                 460

gac gtg tgg atc ggc ttc tcg act gtg cag ggg gtg gag gtg ggc cca    1440
Asp Val Trp Ile Gly Phe Ser Thr Val Gln Gly Val Glu Val Gly Pro
465                 470                 475                 480

gcg ccg cag ggc gag gcc ttc agc ctg gag agc tgc cag aac tgg ctg    1488
Ala Pro Gln Gly Glu Ala Phe Ser Leu Glu Ser Cys Gln Asn Trp Leu
                485                 490                 495

ccc ggg gag cca cac cca gcc aca gcc gag cac tgc gtc cgg ctc ggg    1536
Pro Gly Glu Pro His Pro Ala Thr Ala Glu His Cys Val Arg Leu Gly
            500                 505                 510

ccc acc ggg tgg tgt aac acc gac ctg tgc tca gcg ccg cac agc tac    1584
Pro Thr Gly Trp Cys Asn Thr Asp Leu Cys Ser Ala Pro His Ser Tyr
        515                 520                 525

gtc tgc gag ctg cag ccc gga ggc cca gtg cag gat gcc gag aac ctc    1632
Val Cys Glu Leu Gln Pro Gly Gly Pro Val Gln Asp Ala Glu Asn Leu
    530                 535                 540

ctc gtg gga gcg ccc agt ggg gac ctg cag gga ccc ctg acg cct ctg    1680
Leu Val Gly Ala Pro Ser Gly Asp Leu Gln Gly Pro Leu Thr Pro Leu
545                 550                 555                 560

gca cag cag gac ggc ctc tca gcc ccg cac gag ccc gtg gag gtc atg    1728
Ala Gln Gln Asp Gly Leu Ser Ala Pro His Glu Pro Val Glu Val Met
                565                 570                 575

gta ttc ccg ggc ctg cgt ctg agc cgt gaa gcc ttc ctc acc acg gcc    1776
Val Phe Pro Gly Leu Arg Leu Ser Arg Glu Ala Phe Leu Thr Thr Ala
            580                 585                 590

gaa ttt ggg acc cag gag ctc cgg cgg ccc gcc cag ctg cgg ctg cag    1824
Glu Phe Gly Thr Gln Glu Leu Arg Arg Pro Ala Gln Leu Arg Leu Gln
        595                 600                 605

gtg tac cgg ctc ctc agc aca gca ggg acc ccg gag aac ggc agc gag    1872
Val Tyr Arg Leu Leu Ser Thr Ala Gly Thr Pro Glu Asn Gly Ser Glu
    610                 615                 620

cct gag agc agg tcc ccg gac aac agg acc cag ctg gcc ccc gcg tgc    1920
Pro Glu Ser Arg Ser Pro Asp Asn Arg Thr Gln Leu Ala Pro Ala Cys
625                 630                 635                 640

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Met Pro Gly Gly Arg Trp Cys Pro Gly Ala Asn Ile Cys Leu Pro Leu
                645                 650                 655

gac gcc tcc tgc cac ccc cag gcc tgc gcc aat ggc tgc acg tca ggg    2016
Asp Ala Ser Cys His Pro Gln Ala Cys Ala Asn Gly Cys Thr Ser Gly
            660                 665                 670

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Ser Val Pro Ala Gly Pro Pro Ala Gln Tyr Ser Val Thr Leu His Gly
    690                 695                     700

cag gat gtc ctc atg ctc cct ggt gac ctc gtt ggc ttg cag cac gac    2160
Gln Asp Val Leu Met Leu Pro Gly Asp Leu Val Gly Leu Gln His Asp
705                     710                 715                 720

gct ggc cct ggc gcc ctc ctg cac tgc tcg ccg gct ccc ggc cac cct    2208
Ala Gly Pro Gly Ala Leu Leu His Cys Ser Pro Ala Pro Gly His Pro
                725                 730                     735

ggt ccc cgg gcc ccg tac ctc tcc gcc aac gcc tcg tca tgg ctg ccc    2256
Gly Pro Arg Ala Pro Tyr Leu Ser Ala Asn Ala Ser Ser Trp Leu Pro
            740                 745                     750

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His Leu Pro Ala Gln Leu Glu Gly Thr Trp Gly Cys Pro Ala Cys Ala
        755                     760                     765

ctg cgg ctg ctt gca caa cgg gaa cag ctc acc gtg ctg ctg ggc ttg    2352
Leu Arg Leu Leu Ala Gln Arg Glu Gln Leu Thr Val Leu Leu Gly Leu
    770                 775                     780

agg ccc aac cct gga ctg cgg ctg cct ggg cgc tat gag gtc cgg gca    2400
Arg Pro Asn Pro Gly Leu Arg Leu Pro Gly Arg Tyr Glu Val Arg Ala
785                     790                 795                 800

gag gtg ggc aat ggc gtg tcc agg cac aac ctc tcc tgc agc ttt gac    2448
Glu Val Gly Asn Gly Val Ser Arg His Asn Leu Ser Cys Ser Phe Asp
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gtg gtc tcc cca gtg gct ggg ctg cgg gtc atc tac cct gcc ccc cgc    2496
Val Val Ser Pro Val Ala Gly Leu Arg Val Ile Tyr Pro Ala Pro Arg
            820                 825                     830

gac ggc cgc ctc tac gtg ccc acc aac ggc tca gcc ttg gtg ctc cag    2544
Asp Gly Arg Leu Tyr Val Pro Thr Asn Gly Ser Ala Leu Val Leu Gln
        835                     840                     845

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Val Asp Ser Gly Ala Asn Ala Thr Ala Thr Ala Arg Trp Pro Gly Gly
    850                 855                     860

agt ctc agc gcc cgc ttt gag aat gtc tgc cct gcc ctg gtg gcc acc    2640
Ser Leu Ser Ala Arg Phe Glu Asn Val Cys Pro Ala Leu Val Ala Thr
865                     870                 875                 880

ttc gtg ccc gcc tgc ccc tgg gag acc aac gat acc ctg ttc tca gtg    2688
Phe Val Pro Ala Cys Pro Trp Glu Thr Asn Asp Thr Leu Phe Ser Val
                885                 890                     895

gta gca ctg ccg tgg ctc agt gag ggg gag cac gtg gtg gac gtg gtg    2736
Val Ala Leu Pro Trp Leu Ser Glu Gly Glu His Val Val Asp Val Val
            900                 905                     910

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Val Glu Asn Ser Ala Ser Arg Ala Asn Leu Ser Leu Arg Val Thr Ala
        915                     920                     925

gag gag ccc atc tgt ggc ctc cgc gcc acg ccc agc ccc gag gcc cgt    2832
Glu Glu Pro Ile Cys Gly Leu Arg Ala Thr Pro Ser Pro Glu Ala Arg
    930                 935                     940

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945 950 955 960

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Ser Asp Met Val Phe Arg Trp Thr Ile Asn Asp Lys Gln Ser Leu Thr
965 970 975

ttc cag aac gtg gtc ttc aat gtc att tat cag agc gcg gcg gtc ttc 2976
Phe Gln Asn Val Val Phe Asn Val Ile Tyr Gln Ser Ala Ala Val Phe
980 985 990

aag ctc tca ctg acg gcc tcc aac cac gtg agc aac gtc acc gtg aac 3024
Lys Leu Ser Leu Thr Ala Ser Asn His Val Ser Asn Val Thr Val Asn
995 1000 1005

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Tyr Asn Val Thr Val Glu Arg Met Asn Arg Met Gln Gly Leu Gln Val
1010 1015 1020

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Ser Thr Val Pro Ala Val Leu Ser Pro Asn Ala Thr Leu Ala Leu Thr
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1045 1050 1055

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1060 1065 1070

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Glu Ser Phe Pro Val Pro Asp Pro Ser Val Ala Gln Val Leu Val Glu
1075 1080 1085

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His Asn Val Thr His Thr Tyr Ala Ala Pro Gly Glu Tyr Leu Leu Thr
1090 1095 1100

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Val Leu Ala Ser Asn Ala Phe Glu Asn Leu Thr Gln Gln Val Pro Val
1105 1110 1115 1120

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1125 1130 1135

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1155 1160 1165

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1170 1175 1180

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gtg gac atg agc ctg gcc gtg gag cag ggc gcc ccc gtg gtg gtc agc    3696
Val Asp Met Ser Leu Ala Val Glu Gln Gly Ala Pro Val Val Val Ser
            1220                1225                1230

gcc gcg gtg cag acg ggc gac aac atc acg tgg acc ttc gac atg ggg    3744
Ala Ala Val Gln Thr Gly Asp Asn Ile Thr Trp Thr Phe Asp Met Gly
        1235                1240                1245

gac ggc acc gtg ctg tcg ggc ccg gag gca aca gtg gag cat gtg tac    3792
Asp Gly Thr Val Leu Ser Gly Pro Glu Ala Thr Val Glu His Val Tyr
    1250                1255                1260

ctg cgg gca cag aac tgc aca gtg acc gtg ggt gcg ggc agc ccc gcc    3840
Leu Arg Ala Gln Asn Cys Thr Val Thr Val Gly Ala Gly Ser Pro Ala
1265                1270                1275                1280

ggc cac ctg gcc cgg agc ctg cac gtg ctg gtc ttc gtc ctg gag gtg    3888
Gly His Leu Ala Arg Ser Leu His Val Leu Val Phe Val Leu Glu Val
                1285                1290                1295

ctg cgc gtt gaa ccc gcc gcc tgc atc ccc acg cag cct gac gcg cgg    3936
Leu Arg Val Glu Pro Ala Ala Cys Ile Pro Thr Gln Pro Asp Ala Arg
            1300                1305                1310

ctc acg gcc tac gtc acc ggg aac ccg gcc cac tac ctc ttc gac tgg    3984
Leu Thr Ala Tyr Val Thr Gly Asn Pro Ala His Tyr Leu Phe Asp Trp
        1315                1320                1325

acc ttc ggg gat ggc tcc tcc aac acg acc gtg cgg ggg tgc ccg acg    4032
Thr Phe Gly Asp Gly Ser Ser Asn Thr Thr Val Arg Gly Cys Pro Thr
    1330                1335                1340

gtg aca cac aac ttc acg cgg agc ggc acg ttc ccc ctg gcg ctg gtg    4080
Val Thr His Asn Phe Thr Arg Ser Gly Thr Phe Pro Leu Ala Leu Val
1345                1350                1355                1360

ctg tcc agc cgc gtg aac agg gcg cat tac ttc acc agc atc tgc gtg    4128
Leu Ser Ser Arg Val Asn Arg Ala His Tyr Phe Thr Ser Ile Cys Val
                1365                1370                1375

gag cca gag gtg ggc aac gtc acc ctg cag cca gag agg cag ttt gtg    4176
Glu Pro Glu Val Gly Asn Val Thr Leu Gln Pro Glu Arg Gln Phe Val
            1380                1385                1390

cag ctc ggg gac gag gcc tgg ctg gtg gca tgt gcc tgg ccc ccg ttc    4224
Gln Leu Gly Asp Glu Ala Trp Leu Val Ala Cys Ala Trp Pro Pro Phe
        1395                1400                1405

ccc tac cgc tac acc tgg gac ttt ggc acc gag gaa gcc gcc ccc acc    4272
Pro Tyr Arg Tyr Thr Trp Asp Phe Gly Thr Glu Glu Ala Ala Pro Thr
    1410                1415                1420

cgt gcc agg ggc cct gag gtg acg ttc atc tac cga gac cca ggc tcc    4320
Arg Ala Arg Gly Pro Glu Val Thr Phe Ile Tyr Arg Asp Pro Gly Ser
1425                1430                1435                1440

tat ctt gtg aca gtc acc gcg tcc aac aac atc tct gct gcc aat gac    4368
Tyr Leu Val Thr Val Thr Ala Ser Asn Asn Ile Ser Ala Ala Asn Asp
                1445                1450                1455

tca gcc ctg gtg gag gtg cag gag ccc gtg ctg gtc acc agc atc aag    4416
Ser Ala Leu Val Glu Val Gln Glu Pro Val Leu Val Thr Ser Ile Lys
            1460                1465                1470

gtc aat ggc tcc ctt ggg ctg gag ctg cag cag ccg tac ctg ttc tct    4464
Val Asn Gly Ser Leu Gly Leu Glu Leu Gln Gln Pro Tyr Leu Phe Ser
        1475                1480                1485
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gct gtg ggc cgt ggg cgc ccc gcc agc tac ctg tgg gat ctg ggg gac    4512
Ala Val Gly Arg Gly Arg Pro Ala Ser Tyr Leu Trp Asp Leu Gly Asp
   1490                1495                1500

ggt ggg tgg ctc gag ggt ccg gag gtc acc cac gct tac aac agc aca    4560
Gly Gly Trp Leu Glu Gly Pro Glu Val Thr His Ala Tyr Asn Ser Thr
1505                1510                1515                1520

ggt gac ttc acc gtt agg gtg gcc ggc tgg aat gag gtg agc cgc agc    4608
Gly Asp Phe Thr Val Arg Val Ala Gly Trp Asn Glu Val Ser Arg Ser
                1525                1530                1535

gag gcc tgg ctc aat gtg acg gtg aag cgg cgc gtg cgg ggg ctc gtc    4656
Glu Ala Trp Leu Asn Val Thr Val Lys Arg Arg Val Arg Gly Leu Val
            1540                1545                1550

gtc aat gca agc cgc acg gtg gtg ccc ctg aat ggg agc gtg agc ttc    4704
Val Asn Ala Ser Arg Thr Val Val Pro Leu Asn Gly Ser Val Ser Phe
        1555                1560                1565

agc acg tcg ctg gag gcc ggc agt gat gtg cgc tat tcc tgg gtg ctc    4752
Ser Thr Ser Leu Glu Ala Gly Ser Asp Val Arg Tyr Ser Trp Val Leu
    1570                1575                1580

tgt gac cgc tgc acg ccc atc cct ggg ggt cct acc atc tct tac acc    4800
Cys Asp Arg Cys Thr Pro Ile Pro Gly Gly Pro Thr Ile Ser Tyr Thr
1585                1590                1595                1600

ttc cgc tcc gtg ggc acc ttc aat atc atc gtc acg gct gag aac gag    4848
Phe Arg Ser Val Gly Thr Phe Asn Ile Ile Val Thr Ala Glu Asn Glu
                1605                1610                1615

gtg ggc tcc gcc cag gac agc atc ttc gtc tat gtc ctg cag ctc ata    4896
Val Gly Ser Ala Gln Asp Ser Ile Phe Val Tyr Val Leu Gln Leu Ile
            1620                1625                1630

gag ggg ctg cag gtg gtg ggc ggt ggc cgc tac ttc ccc acc aac cac    4944
Glu Gly Leu Gln Val Val Gly Gly Gly Arg Tyr Phe Pro Thr Asn His
        1635                1640                1645

acg gta cag ctg cag gcc gtg gtt agg gat ggc acc aac gtc tcc tac    4992
Thr Val Gln Leu Gln Ala Val Val Arg Asp Gly Thr Asn Val Ser Tyr
    1650                1655                1660

agc tgg act gcc tgg agg gac agg ggc ccg gcc ctg gcc ggc agc ggc    5040
Ser Trp Thr Ala Trp Arg Asp Arg Gly Pro Ala Leu Ala Gly Ser Gly
1665                1670                1675                1680

aaa ggc ttc tcg ctc acc gtg ctc gag gcc ggc acc tac cat gtg cag    5088
Lys Gly Phe Ser Leu Thr Val Leu Glu Ala Gly Thr Tyr His Val Gln
                1685                1690                1695

ctg cgg gcc acc aac atg ctg ggc agc gcc tgg gcc gac tgc acc atg    5136
Leu Arg Ala Thr Asn Met Leu Gly Ser Ala Trp Ala Asp Cys Thr Met
            1700                1705                1710

gac ttc gtg gag cct gtg ggg tgg ctg atg gtg gcc gcc tcc ccg aac    5184
Asp Phe Val Glu Pro Val Gly Trp Leu Met Val Ala Ala Ser Pro Asn
        1715                1720                1725

cca gct gcc gtc aac aca agc gtc acc ctc agt gcc gag ctg gct ggt    5232
Pro Ala Ala Val Asn Thr Ser Val Thr Leu Ser Ala Glu Leu Ala Gly
    1730                1735                1740

ggc agt ggt gtc gta tac act tgg tcc ttg gag gag ggg ctg agc tgg    5280
Gly Ser Gly Val Val Tyr Thr Trp Ser Leu Glu Glu Gly Leu Ser Trp
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1745 1750 1755 1760

gag acc tcc gag cca ttt acc acc cat agc ttc ccc aca ccc ggc ctg 5328
Glu Thr Ser Glu Pro Phe Thr Thr His Ser Phe Pro Thr Pro Gly Leu
1765 1770 1775

cac ttg gtc acc atg acg gca ggg aac ccg ctg ggc tca gcc aac gcc 5376
His Leu Val Thr Met Thr Ala Gly Asn Pro Leu Gly Ser Ala Asn Ala
1780 1785 1790

acc gtg gaa gtg gat gtg cag gtg cct gtg agt ggc ctc agc atc agg 5424
Thr Val Glu Val Asp Val Gln Val Pro Val Ser Gly Leu Ser Ile Arg
1795 1800 1805

gcc agc gag ccc gga ggc agc ttc gtg gcg gcc ggg tcc tct gtg ccc 5472
Ala Ser Glu Pro Gly Gly Ser Phe Val Ala Ala Gly Ser Ser Val Pro
1810 1815 1820

ttt tgg ggg cag ctg gcc acg ggc acc aat gtg agc tgg tgc tgg gct 5520
Phe Trp Gly Gln Leu Ala Thr Gly Thr Asn Val Ser Trp Cys Trp Ala
1825 1830 1835 1840

gtg ccc ggc ggc agc agc aag cgt ggc cct cat gtc acc atg gtc ttc 5568
Val Pro Gly Gly Ser Ser Lys Arg Gly Pro His Val Thr Met Val Phe
1845 1850 1855

ccg gat gct ggc acc ttc tcc atc cgg ctc aat gcc tcc aac gca gtc 5616
Pro Asp Ala Gly Thr Phe Ser Ile Arg Leu Asn Ala Ser Asn Ala Val
1860 1865 1870

agc tgg gtc tca gcc acg tac aac ctc acg gcg gag gag ccc atc gtg 5664
Ser Trp Val Ser Ala Thr Tyr Asn Leu Thr Ala Glu Glu Pro Ile Val
1875 1880 1885

ggc ctg gtg ctg tgg gcc agc agc aag gtg gtg gcg ccc ggg cag ctg 5712
Gly Leu Val Leu Trp Ala Ser Ser Lys Val Val Ala Pro Gly Gln Leu
1890 1895 1900

gtc cat ttt cag atc ctg ctg gct gcc ggc tca gct gtc acc ttc cgc 5760
Val His Phe Gln Ile Leu Leu Ala Ala Gly Ser Ala Val Thr Phe Arg
1905 1910 1915 1920

cta cag gtc ggc ggg gcc aac ccc gag gtg ctc ccc ggg ccc cgt ttc 5808
Leu Gln Val Gly Gly Ala Asn Pro Glu Val Leu Pro Gly Pro Arg Phe
1925 1930 1935

tcc cac agc ttc ccc cgc gtc gga gac cac gtg gtg agc gtg cgg ggc 5856
Ser His Ser Phe Pro Arg Val Gly Asp His Val Val Ser Val Arg Gly
1940 1945 1950

aaa aac cac gtg agc tgg gcc cag gcg cag gtg cgc atc gtg gtg ctg 5904
Lys Asn His Val Ser Trp Ala Gln Ala Gln Val Arg Ile Val Val Leu
1955 1960 1965

gag gcc gtg agt ggg ctg cag gtg ccc aac tgc tgc gag cct ggc atc 5952
Glu Ala Val Ser Gly Leu Gln Val Pro Asn Cys Cys Glu Pro Gly Ile
1970 1975 1980

gcc acg ggc act gag agg aac ttc aca gcc cgc gtg cag cgc ggc tct 6000
Ala Thr Gly Thr Glu Arg Asn Phe Thr Ala Arg Val Gln Arg Gly Ser
1985 1990 1995 2000

cgg gtc gcc tac gcc tgg tac ttc tcg ctg cag aag gtc cag ggc gac 6048
Arg Val Ala Tyr Ala Trp Tyr Phe Ser Leu Gln Lys Val Gln Gly Asp
2005 2010 2015

tcg ctg gtc atc ctg tcg ggc cgc gac gtc acc tac acg ccc gtg gcc 6096

Ser Leu Val Ile Leu Ser Gly Arg Asp Val Thr Tyr Thr Pro Val Ala
2020 2025 2030

gcg ggg ctg ttg gag atc cag gtg cgc gcc ttc aac gcc ctg ggc agt 6144
Ala Gly Leu Leu Glu Ile Gln Val Arg Ala Phe Asn Ala Leu Gly Ser
2035 2040 2045

gag aac cgc acg ctg gtg ctg gag gtt cag gac gcc gtc cag tat gtg 6192
Glu Asn Arg Thr Leu Val Leu Glu Val Gln Asp Ala Val Gln Tyr Val
2050 2055 2060

gcc ctg cag agc ggc ccc tgc ttc acc aac cgc tcg gcg cag ttt gag 6240
Ala Leu Gln Ser Gly Pro Cys Phe Thr Asn Arg Ser Ala Gln Phe Glu
2065 2070 2075 2080

gcc gcc acc agc ccc agc ccc cgg cgt gtg gcc tac cac tgg gac ttt 6288
Ala Ala Thr Ser Pro Ser Pro Arg Arg Val Ala Tyr His Trp Asp Phe
2085 2090 2095

ggg gat ggg tcg cca ggg cag gac aca gat gag ccc agg gcc gag cac 6336
Gly Asp Gly Ser Pro Gly Gln Asp Thr Asp Glu Pro Arg Ala Glu His
2100 2105 2110

tcc tac ctg agg cct ggg gac tac cgc gtg cag gtg aac gcc tcc aac 6384
Ser Tyr Leu Arg Pro Gly Asp Tyr Arg Val Gln Val Asn Ala Ser Asn
2115 2120 2125

ctg gtg agc ttc ttc gtg gcg cag gcc acg gtg acc gtc cag gtg ctg 6432
Leu Val Ser Phe Phe Val Ala Gln Ala Thr Val Thr Val Gln Val Leu
2130 2135 2140

gcc tgc cgg gag ccg gag gtg gac gtg gtc ctg ccc ctg cag gtg ctg 6480
Ala Cys Arg Glu Pro Glu Val Asp Val Val Leu Pro Leu Gln Val Leu
2145 2150 2155 2160

atg cgg cga tca cag cgc aac tac ttg gag gcc cac gtt gac ctg cgc 6528
Met Arg Arg Ser Gln Arg Asn Tyr Leu Glu Ala His Val Asp Leu Arg
2165 2170 2175

gac tgc gtc acc tac cag act gag tac cgc tgg gag gtg tat cgc acc 6576
Asp Cys Val Thr Tyr Gln Thr Glu Tyr Arg Trp Glu Val Tyr Arg Thr
2180 2185 2190

gcc agc tgc cag cgg ccg ggg cgc cca gcg cgt gtg gcc ctg ccc ggc 6624
Ala Ser Cys Gln Arg Pro Gly Arg Pro Ala Arg Val Ala Leu Pro Gly
2195 2200 2205

gtg gac gtg agc cgg cct cgg ctg gtg ctg ccg cgg ctg gcg ctg cct 6672
Val Asp Val Ser Arg Pro Arg Leu Val Leu Pro Arg Leu Ala Leu Pro
2210 2215 2220

gtg ggg cac tac tgc ttt gtg ttt gtc gtg tca ttt ggg gac acg cca 6720
Val Gly His Tyr Cys Phe Val Phe Val Val Ser Phe Gly Asp Thr Pro
2225 2230 2235 2240

ctg aca cag agc atc cag gcc aat gtg acg gtg gcc ccc gag cgc ctg 6768
Leu Thr Gln Ser Ile Gln Ala Asn Val Thr Val Ala Pro Glu Arg Leu
2245 2250 2255

gtg ccc atc att gag ggt ggc tca tac cgc gtg tgg tca gac aca cgg 6816
Val Pro Ile Ile Glu Gly Gly Ser Tyr Arg Val Trp Ser Asp Thr Arg
2260 2265 2270

gac ctg gtg ctg gat ggg agc gag tcc tac gac ccc aac ctg gag gac 6864
Asp Leu Val Leu Asp Gly Ser Glu Ser Tyr Asp Pro Asn Leu Glu Asp
2275 2280 2285

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ggc gac cag acg ccg ctc agt ttc cac tgg gcc tgt gtg gct tcg aca    6912
Gly Asp Gln Thr Pro Leu Ser Phe His Trp Ala Cys Val Ala Ser Thr
   2290                2295                2300

cag agg gag gct ggc ggg tgt gcg ctg aac ttt ggg ccc cgc ggg agc    6960
Gln Arg Glu Ala Gly Gly Cys Ala Leu Asn Phe Gly Pro Arg Gly Ser
2305                2310                2315                2320

agc acg gtc acc att cca cgg gag cgg ctg gcg gct ggc gtg gag tac    7008
Ser Thr Val Thr Ile Pro Arg Glu Arg Leu Ala Ala Gly Val Glu Tyr
               2325                2330                2335

acc ttc agc ctg acc gtg tgg aag gcc ggc cgc aag gag gag gcc acc    7056
Thr Phe Ser Leu Thr Val Trp Lys Ala Gly Arg Lys Glu Glu Ala Thr
           2340                2345                2350

aac cag acg gtg ctg atc cgg agt ggc cgg gtg ccc att gtg tcc ttg    7104
Asn Gln Thr Val Leu Ile Arg Ser Gly Arg Val Pro Ile Val Ser Leu
       2355                2360                2365

gag tgt gtg tcc tgc aag gca cag gcc gtg tac gaa gtg agc cgc agc    7152
Glu Cys Val Ser Cys Lys Ala Gln Ala Val Tyr Glu Val Ser Arg Ser
   2370                2375                2380

tcc tac gtg tac ttg gag ggc cgc tgc ctc aat tgc agc agc ggc tcc    7200
Ser Tyr Val Tyr Leu Glu Gly Arg Cys Leu Asn Cys Ser Ser Gly Ser
2385                2390                2395                2400

aag cga ggg cgg tgg gct gca cgt acg ttc agc aac aag acg ctg gtg    7248
Lys Arg Gly Arg Trp Ala Ala Arg Thr Phe Ser Asn Lys Thr Leu Val
               2405                2410                2415

ctg gat gag acc acc aca tcc acg ggc agt gca ggc atg cga ctg gtg    7296
Leu Asp Glu Thr Thr Thr Ser Thr Gly Ser Ala Gly Met Arg Leu Val
           2420                2425                2430

ctg cgg cgg ggc gtg ctg cgg gac ggc gag gga tac acc ttc acg ctc    7344
Leu Arg Arg Gly Val Leu Arg Asp Gly Glu Gly Tyr Thr Phe Thr Leu
       2435                2440                2445

acg gtg ctg ggc cgc tct ggc gag gag gag ggc tgc gcc tcc atc cgc    7392
Thr Val Leu Gly Arg Ser Gly Glu Glu Glu Gly Cys Ala Ser Ile Arg
   2450                2455                2460

ctg tcc ccc aac cgc ccg ccg ctg ggg ggc tct tgc cgc ctc ttc cca    7440
Leu Ser Pro Asn Arg Pro Pro Leu Gly Gly Ser Cys Arg Leu Phe Pro
2465                2470                2475                2480

ctg ggc gct gtg cac gcc ctc acc acc aag gtg cac ttc gaa tgc acg    7488
Leu Gly Ala Val His Ala Leu Thr Thr Lys Val His Phe Glu Cys Thr
               2485                2490                2495

ggc tgg cat gac gcg gag gat gct ggc gcc ccg ctg gtg tac gcc ctg    7536
Gly Trp His Asp Ala Glu Asp Ala Gly Ala Pro Leu Val Tyr Ala Leu
           2500                2505                2510

ctg ctg cgg cgc tgt cgc cag ggc cac tgc gag gag ttc tgt gtc tac    7584
Leu Leu Arg Arg Cys Arg Gln Gly His Cys Glu Glu Phe Cys Val Tyr
       2515                2520                2525

aag ggc agc ctc tcc agc tac gga gcc gtg ctg ccc ccg ggt ttc agg    7632
Lys Gly Ser Leu Ser Ser Tyr Gly Ala Val Leu Pro Pro Gly Phe Arg
   2530                2535                2540

cca cac ttc gag gtg ggc ctg gcc gtg gtg gtg cag gac cag ctg gga    7680
Pro His Phe Glu Val Gly Leu Ala Val Val Val Gln Asp Gln Leu Gly
2545                2550                2555                2560
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gcc gct gtg gtc gcc ctc aac agg tct ttg gcc atc acc ctc cca gag 7728
Ala Ala Val Val Ala Leu Asn Arg Ser Leu Ala Ile Thr Leu Pro Glu
2565 2570 2575

ccc aac ggc agc gca acg ggg ctc aca gtc tgg ctg cac ggg ctc acc 7776
Pro Asn Gly Ser Ala Thr Gly Leu Thr Val Trp Leu His Gly Leu Thr
2580 2585 2590

gct agt gtg ctc cca ggg ctg ctg cgg cag gcc gat ccc cag cac gtc 7824
Ala Ser Val Leu Pro Gly Leu Leu Arg Gln Ala Asp Pro Gln His Val
2595 2600 2605

atc gag tac tcg ttg gcc ctg gtc acc gtg ctg aac gag tac gag cgg 7872
Ile Glu Tyr Ser Leu Ala Leu Val Thr Val Leu Asn Glu Tyr Glu Arg
2610 2615 2620

gcc ctg gac gtg gcg gca gag ccc aag cac gag cgg cag cac cga gcc 7920
Ala Leu Asp Val Ala Ala Glu Pro Lys His Glu Arg Gln His Arg Ala
2625 2630 2635 2640

cag ata cgc aag aac atc acg gag act ctg gtg tcc ctg agg gtc cac 7968
Gln Ile Arg Lys Asn Ile Thr Glu Thr Leu Val Ser Leu Arg Val His
2645 2650 2655

act gtg gat gac atc cag cag atc gct gct gcg ctg gcc cag tgc atg 8016
Thr Val Asp Asp Ile Gln Gln Ile Ala Ala Ala Leu Ala Gln Cys Met
2660 2665 2670

ggg ccc agc agg gag ctc gta tgc cgc tcg tgc ctg aag cag acg ctg 8064
Gly Pro Ser Arg Glu Leu Val Cys Arg Ser Cys Leu Lys Gln Thr Leu
2675 2680 2685

cac aag ctg gag gcc atg atg ctc atc ctg cag gca gag acc acc gcg 8112
His Lys Leu Glu Ala Met Met Leu Ile Leu Gln Ala Glu Thr Thr Ala
2690 2695 2700

ggc acc gtg acg ccc acc gcc atc gga gac agc atc ctc aac atc aca 8160
Gly Thr Val Thr Pro Thr Ala Ile Gly Asp Ser Ile Leu Asn Ile Thr
2705 2710 2715 2720

gga gac ctc atc cac ctg gcc agc tcg gac gtg cgg gca cca cag ccc 8208
Gly Asp Leu Ile His Leu Ala Ser Ser Asp Val Arg Ala Pro Gln Pro
2725 2730 2735

tca gag ctg gga gcc gag tca cca tct cgg atg gtg gcg tcc cag gcc 8256
Ser Glu Leu Gly Ala Glu Ser Pro Ser Arg Met Val Ala Ser Gln Ala
2740 2745 2750

tac aac ctg acc tct gcc ctc atg cgc atc ctc atg cgc tcc cgc gtg 8304
Tyr Asn Leu Thr Ser Ala Leu Met Arg Ile Leu Met Arg Ser Arg Val
2755 2760 2765

ctc aac gag gag ccc ctg acg ctg gcg ggc gag gag atc gtg gcc cag 8352
Leu Asn Glu Glu Pro Leu Thr Leu Ala Gly Glu Glu Ile Val Ala Gln
2770 2775 2780

ggc aag cgc tcg gac ccg cgg agc ctg ctg tgc tat ggc ggc gcc cca 8400
Gly Lys Arg Ser Asp Pro Arg Ser Leu Leu Cys Tyr Gly Gly Ala Pro
2785 2790 2795 2800

ggg cct ggc tgc cac ttc tcc atc ccc gag gct ttc agc ggg gcc ctg 8448
Gly Pro Gly Cys His Phe Ser Ile Pro Glu Ala Phe Ser Gly Ala Leu
2805 2810 2815

gcc aac ctc agt gac gtg gtg cag ctc atc ttt ctg gtg gac tcc aat 8496
Ala Asn Leu Ser Asp Val Val Gln Leu Ile Phe Leu Val Asp Ser Asn

2820 2825 2830

ccc ttt ccc ttt ggc tat atc agc aac tac acc gtc tcc acc aag gtg 8544
Pro Phe Pro Phe Gly Tyr Ile Ser Asn Tyr Thr Val Ser Thr Lys Val
2835 2840 2845

gcc tcg atg gca ttc cag aca cag gcc ggc gcc cag atc ccc atc gag 8592
Ala Ser Met Ala Phe Gln Thr Gln Ala Gly Ala Gln Ile Pro Ile Glu
2850 2855 2860

cgg ctg gcc tca gag cgc gcc atc acc gtg aag gtg ccc aac aac tcg 8640
Arg Leu Ala Ser Glu Arg Ala Ile Thr Val Lys Val Pro Asn Asn Ser
2865 2870 2875 2880

gac tgg gct gcc cgg ggc cac cgc agc tcc gcc aac tcc gcc aac tcc 8688
Asp Trp Ala Ala Arg Gly His Arg Ser Ser Ala Asn Ser Ala Asn Ser
2885 2890 2895

gtt gtg gtc cag ccc cag gcc tcc gtc ggt gct gtg gtc acc ctg gac 8736
Val Val Val Gln Pro Gln Ala Ser Val Gly Ala Val Val Thr Leu Asp
2900 2905 2910

agc agc aac cct gcg gcc ggg ctg cat ctg cag ctc aac tat acg ctg 8784
Ser Ser Asn Pro Ala Ala Gly Leu His Leu Gln Leu Asn Tyr Thr Leu
2915 2920 2925

ctg gac ggc cac tac ctg tct gag gaa cct gag ccc tac ctg gca gtc 8832
Leu Asp Gly His Tyr Leu Ser Glu Glu Pro Glu Pro Tyr Leu Ala Val
2930 2935 2940

tac cta cac tcg gag ccc cgg ccc aat gag cac aac tgc tcg gct agc 8880
Tyr Leu His Ser Glu Pro Arg Pro Asn Glu His Asn Cys Ser Ala Ser
2945 2950 2955 2960

agg agg atc cgc cca gag tca ctc cag ggt gct gac cac cgg ccc tac 8928
Arg Arg Ile Arg Pro Glu Ser Leu Gln Gly Ala Asp His Arg Pro Tyr
2965 2970 2975

acc ttc ttc att tcc ccg ggg agc aga gac cca gcg ggg agt tac cat 8976
Thr Phe Phe Ile Ser Pro Gly Ser Arg Asp Pro Ala Gly Ser Tyr His
2980 2985 2990

ctg aac ctc tcc agc cac ttc cgc tgg tcg gcg ctg cag gtg tcc gtg 9024
Leu Asn Leu Ser Ser His Phe Arg Trp Ser Ala Leu Gln Val Ser Val
2995 3000 3005

ggc ctg tac acg tcc ctg tgc cag tac ttc agc gag gag gac atg gtg 9072
Gly Leu Tyr Thr Ser Leu Cys Gln Tyr Phe Ser Glu Glu Asp Met Val
3010 3015 3020

tgg cgg aca gag ggg ctg ctg ccc ctg gag gag acc tcg ccc cgc cag 9120
Trp Arg Thr Glu Gly Leu Leu Pro Leu Glu Glu Thr Ser Pro Arg Gln
3025 3030 3035 3040

gcc gtc tgc ctc acc cgc cac ctc acc gcc ttc ggc gcc agc ctc ttc 9168
Ala Val Cys Leu Thr Arg His Leu Thr Ala Phe Gly Ala Ser Leu Phe
3045 3050 3055

gtg ccc cca agc cat gtc cgc ttt gtg ttt cct gag ccg aca gcg gat 9216
Val Pro Pro Ser His Val Arg Phe Val Phe Pro Glu Pro Thr Ala Asp
3060 3065 3070

gta aac tac atc gtc atg ctg aca tgt gct gtg tgc ctg gtg acc tac 9264
Val Asn Tyr Ile Val Met Leu Thr Cys Ala Val Cys Leu Val Thr Tyr
3075 3080 3085

atg gtc atg gcc gcc atc ctg cac aag ctg gac cag ttg gat gcc agc 9312

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Met Val Met Ala Ala Ile Leu His Lys Leu Asp Gln Leu Asp Ala Ser
    3090                3095                3100

cgg ggc cgc gcc atc cct ttc tgt ggg cag cgg ggc cgc ttc aag tac     9360
Arg Gly Arg Ala Ile Pro Phe Cys Gly Gln Arg Gly Arg Phe Lys Tyr
3105                3110                3115                3120

gag atc ctc gtc aag aca ggc tgg ggc cgg ggc tca ggt acc acg gcc     9408
Glu Ile Leu Val Lys Thr Gly Trp Gly Arg Gly Ser Gly Thr Thr Ala
                3125                3130                3135

cac gtg ggc atc atg ctg tat ggg gtg gac agc cgg agc ggc cac cgg     9456
His Val Gly Ile Met Leu Tyr Gly Val Asp Ser Arg Ser Gly His Arg
            3140                3145                3150

cac ctg gac ggc gac aga gcc ttc cac cgc aac agc ctg gac atc ttc     9504
His Leu Asp Gly Asp Arg Ala Phe His Arg Asn Ser Leu Asp Ile Phe
        3155                3160                3165

cgg atc gcc acc ccg cac agc ctg ggt agc gtg tgg aag atc cga gtg     9552
Arg Ile Ala Thr Pro His Ser Leu Gly Ser Val Trp Lys Ile Arg Val
    3170                3175                3180

tgg cac gac aac aaa ggg ctc agc cct gcc tgg ttc ctg cag cac gtc     9600
Trp His Asp Asn Lys Gly Leu Ser Pro Ala Trp Phe Leu Gln His Val
3185                3190                3195                3200

atc gtc agg gac ctg cag acg gca cgc agc gcc ttc ttc ctg gtc aat     9648
Ile Val Arg Asp Leu Gln Thr Ala Arg Ser Ala Phe Phe Leu Val Asn
                3205                3210                3215

gac tgg ctt tcg gtg gag acg gag gcc aac ggg ggc ctg gtg gag aag     9696
Asp Trp Leu Ser Val Glu Thr Glu Ala Asn Gly Gly Leu Val Glu Lys
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gag gtg ctg gcc gcg agc gac gca gcc ctt ttg cgc ttc cgg cgc ctg     9744
Glu Val Leu Ala Ala Ser Asp Ala Ala Leu Leu Arg Phe Arg Arg Leu
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ctg gtg gct gag ctg cag cgt ggc ttc ttt gac aag cac atc tgg ctc     9792
Leu Val Ala Glu Leu Gln Arg Gly Phe Phe Asp Lys His Ile Trp Leu
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tcc ata tgg gac cgg ccg cct cgt agc cgt ttc act cgc atc cag agg     9840
Ser Ile Trp Asp Arg Pro Pro Arg Ser Arg Phe Thr Arg Ile Gln Arg
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gcc acc tgc tgc gtt ctc ctc atc tgc ctc ttc ctg ggc gcc aac gcc     9888
Ala Thr Cys Cys Val Leu Leu Ile Cys Leu Phe Leu Gly Ala Asn Ala
                3285                3290                3295

gtg tgg tac ggg gct gtt ggc gac tct gcc tac agc acg ggg cat gtg     9936
Val Trp Tyr Gly Ala Val Gly Asp Ser Ala Tyr Ser Thr Gly His Val
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tcc agg ctg agc ccg ctg agc gtc gac aca gtc gct gtt ggc ctg gtg     9984
Ser Arg Leu Ser Pro Leu Ser Val Asp Thr Val Ala Val Gly Leu Val
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Ser Ser Val Val Val Tyr Pro Val Tyr Leu Ala Ile Leu Phe Leu Phe
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cgg atg tcc cgg agc aag gtg gct ggg agc ccg agc ccc aca cct gcc     10080
Arg Met Ser Arg Ser Lys Val Ala Gly Ser Pro Ser Pro Thr Pro Ala
3345                3350                3355                3360
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Gly Gln Gln Val Leu Asp Ile Asp Ser Cys Leu Asp Ser Ser Val Leu
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gac agc tcc ttc ctc acg ttc tca ggc ctc cac gct gag cag gcc ttt    10176
Asp Ser Ser Phe Leu Thr Phe Ser Gly Leu His Ala Glu Gln Ala Phe
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gtt gga cag atg aag agt gac ttg ttt ctg gat gat tct aag agt ctg    10224
Val Gly Gln Met Lys Ser Asp Leu Phe Leu Asp Asp Ser Lys Ser Leu
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Val Cys Trp Pro Ser Gly Glu Gly Thr Leu Ser Trp Pro Asp Leu Leu
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Ser Asp Pro Ser Ile Val Gly Ser Asn Leu Arg Gln Leu Ala Arg Gly
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Gln Ala Gly His Gly Leu Gly Pro Glu Glu Asp Gly Phe Ser Leu Ala
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Ser Pro Tyr Ser Pro Ala Lys Ser Phe Ser Ala Ser Asp Glu Asp Leu
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atc cag cag gtc ctt gcc gag ggg gtc agc agc cca gcc cct acc caa    10464
Ile Gln Gln Val Leu Ala Glu Gly Val Ser Ser Pro Ala Pro Thr Gln
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gac acc cac atg gaa acg gac ctg ctc agc agc ctg tcc agc act cct    10512
Asp Thr His Met Glu Thr Asp Leu Leu Ser Ser Leu Ser Ser Thr Pro
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ggg gag aag aca gag acg ctg gcg ctg cag agg ctg ggg gag ctg ggg    10560
Gly Glu Lys Thr Glu Thr Leu Ala Leu Gln Arg Leu Gly Glu Leu Gly
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cca ccc agc cca ggc ctg aac tgg gaa cag ccc cag gca gcg agg ctg    10608
Pro Pro Ser Pro Gly Leu Asn Trp Glu Gln Pro Gln Ala Ala Arg Leu
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tcc agg aca gga ctg gtg gag ggt ctg cgg aag cgc ctg ctg ccg gcc    10656
Ser Arg Thr Gly Leu Val Glu Gly Leu Arg Lys Arg Leu Leu Pro Ala
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tgg tgt gcc tcc ctg gcc cac ggg ctc agc ctg ctc ctg gtg gct gtg    10704
Trp Cys Ala Ser Leu Ala His Gly Leu Ser Leu Leu Leu Val Ala Val
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Ala Val Ala Val Ser Gly Trp Val Gly Ala Ser Phe Pro Pro Gly Val
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agt gtt gcg tgg ctc ctg tcc agc agc gcc agc ttc ctg gcc tca ttc    10800
Ser Val Ala Trp Leu Leu Ser Ser Ser Ala Ser Phe Leu Ala Ser Phe
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ctc ggc tgg gag cca ctg aag gtc ttg ctg gaa gcc ctg tac ttc tca    10848
Leu Gly Trp Glu Pro Leu Lys Val Leu Leu Glu Ala Leu Tyr Phe Ser
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ctg gtg gcc aag cgg ctg cac ccg gat gaa gat gac acc ctg gta gag    10896
Leu Val Ala Lys Arg Leu His Pro Asp Glu Asp Asp Thr Leu Val Glu
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ccc cac ggc ttt gca ctc ttc ctg gcc aag gaa gaa gcc cgc aag gtc 10992
Pro His Gly Phe Ala Leu Phe Leu Ala Lys Glu Glu Ala Arg Lys Val
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aag agg cta cat ggc atg ctg cgg agc ctc ctg gtg tac atg ctt ttt 11040
Lys Arg Leu His Gly Met Leu Arg Ser Leu Leu Val Tyr Met Leu Phe
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Leu Leu Val Thr Leu Leu Ala Ser Tyr Gly Asp Ala Ser Cys His Gly
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His Ala Tyr Arg Leu Gln Ser Ala Ile Lys Gln Glu Leu His Ser Arg
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Ala Phe Leu Ala Ile Thr Arg Ser Glu Glu Leu Trp Pro Trp Met Ala
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His Val Leu Leu Pro Tyr Val His Gly Asn Gln Ser Ser Pro Glu Leu
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Gly Pro Pro Arg Leu Arg Gln Val Arg Leu Gln Glu Ala Leu Tyr Pro
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Asp Pro Pro Gly Pro Arg Val His Thr Cys Ser Ala Ala Gly Gly Phe
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Ser Thr Ser Asp Tyr Asp Val Gly Trp Glu Ser Pro His Asn Gly Ser
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Tyr Ser Pro Ala Val Gly Leu His Ala Ala Val Thr Leu Arg Leu Glu
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Val Cys Leu Leu Leu Phe Ala Val His Phe Ala Val Ala Glu Ala Arg
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Ser Ala Ala Arg Gly Leu Ala Ala Ser Leu Leu Phe Leu Leu Leu Val
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Lys Thr Leu Cys Arg Ala Leu Pro Glu Leu Leu Gly Val Thr Leu Gly
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Leu Arg Gly Glu Leu Tyr Arg Pro Ala Trp Glu Pro Gln Asp Tyr Glu
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Met Val Glu Leu Phe Leu Arg Arg Leu Arg Leu Trp Met Gly Leu Ser
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Lys Val Lys Glu Phe Arg His Lys Val Arg Phe Glu Gly Met Glu Pro
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Leu Pro Ser Arg Ser Ser Arg Gly Ser Lys Val Ser Pro Asp Val Pro
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Cys Glu Pro Pro Cys Leu Cys Gly Pro Ala Pro Gly Ala Ala Cys Arg
35 40 45

Val Asn Cys Ser Gly Arg Gly Leu Arg Thr Leu Gly Pro Ala Leu Arg
50 55 60

Ile Pro Ala Asp Ala Thr Glu Leu Asp Val Ser His Asn Leu Leu Arg
65 70 75 80

Ala Leu Asp Val Gly Leu Leu Ala Asn Leu Ser Ala Leu Ala Glu Leu
85 90 95

Asp Ile Ser Asn Asn Lys Ile Ser Thr Leu Glu Glu Gly Ile Phe Ala
100 105 110

Asn Leu Phe Asn Leu Ser Glu Ile Asn Leu Ser Gly Asn Pro Phe Glu
115 120 125

Cys Asp Cys Gly Leu Ala Trp Leu Pro Gln Trp Ala Glu Glu Gln Gln

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Val Arg Val Val Gln Pro Glu Ala Ala Thr Cys Ala Gly Pro Gly Ser
145                 150                 155                 160

Leu Ala Gly Gln Pro Leu Leu Gly Ile Pro Leu Leu Asp Ser Gly Cys
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Gly Glu Glu Tyr Val Ala Cys Leu Pro Asp Asn Ser Ser Gly Thr Val
            180                 185                 190

Ala Ala Val Ser Phe Ser Ala Ala His Glu Gly Leu Leu Gln Pro Glu
        195                 200                 205

Ala Cys Ser Ala Phe Cys Phe Ser Thr Gly Gln Gly Leu Ala Ala Leu
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Ser Glu Gln Gly Trp Cys Leu Cys Gly Ala Ala Gln Pro Ser Ser Ala
225                 230                 235                 240

Ser Phe Ala Cys Leu Ser Leu Cys Ser Gly Pro Pro Ala Pro Pro Ala
                245                 250                 255

Pro Thr Cys Arg Gly Pro Thr Leu Leu Gln His Val Phe Pro Ala Ser
            260                 265                 270

Pro Gly Ala Thr Leu Val Gly Pro His Gly Pro Leu Ala Ser Gly Gln
        275                 280                 285

Leu Ala Ala Phe His Ile Ala Ala Pro Leu Pro Val Thr Asp Thr Arg
    290                 295                 300

Trp Asp Phe Gly Asp Gly Ser Ala Glu Val Asp Ala Ala Gly Pro Ala
305                 310                 315                 320

Ala Ser His Arg Tyr Val Leu Pro Gly Arg Tyr His Val Thr Ala Val
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Leu Ala Leu Gly Ala Gly Ser Ala Leu Leu Gly Thr Asp Val Gln Val
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Glu Ala Ala Pro Ala Ala Leu Glu Leu Val Cys Pro Ser Ser Val Gln
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Ser Asp Glu Ser Leu Asp Leu Ser Ile Gln Asn Arg Gly Gly Ser Gly
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Leu Glu Ala Ala Tyr Ser Ile Val Ala Leu Gly Glu Glu Pro Ala Arg
385                 390                 395                 400

Ala Val His Pro Leu Cys Pro Ser Asp Thr Glu Ile Phe Pro Gly Asn
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Gly His Cys Tyr Arg Leu Val Val Glu Lys Ala Ala Trp Leu Gln Ala
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Gln Glu Gln Cys Gln Ala Trp Ala Gly Ala Ala Leu Ala Met Val Asp
        435                 440                 445

Ser Pro Ala Val Gln Arg Phe Leu Val Ser Arg Val Thr Arg Ser Leu
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Asp Val Trp Ile Gly Phe Ser Thr Val Gln Gly Val Glu Val Gly Pro
465                 470                 475                 480

Ala Pro Gln Gly Glu Ala Phe Ser Leu Glu Ser Cys Gln Asn Trp Leu
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Pro Gly Glu Pro His Pro Ala Thr Ala Glu His Cys Val Arg Leu Gly
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Pro Thr Gly Trp Cys Asn Thr Asp Leu Cys Ser Ala Pro His Ser Tyr
515 520 525

Val Cys Glu Leu Gln Pro Gly Gly Pro Val Gln Asp Ala Glu Asn Leu
530 535 540

Leu Val Gly Ala Pro Ser Gly Asp Leu Gln Gly Pro Leu Thr Pro Leu
545 550 555 560

Ala Gln Gln Asp Gly Leu Ser Ala Pro His Glu Pro Val Glu Val Met
565 570 575

Val Phe Pro Gly Leu Arg Leu Ser Arg Glu Ala Phe Leu Thr Thr Ala
580 585 590

Glu Phe Gly Thr Gln Glu Leu Arg Arg Pro Ala Gln Leu Arg Leu Gln
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Val Tyr Arg Leu Leu Ser Thr Ala Gly Thr Pro Glu Asn Gly Ser Glu
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Pro Glu Ser Arg Ser Pro Asp Asn Arg Thr Gln Leu Ala Pro Ala Cys
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Met Pro Gly Gly Arg Trp Cys Pro Gly Ala Asn Ile Cys Leu Pro Leu
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Asp Ala Ser Cys His Pro Gln Ala Cys Ala Asn Gly Cys Thr Ser Gly
660 665 670

Pro Gly Leu Pro Gly Ala Pro Tyr Ala Leu Trp Arg Glu Phe Leu Phe
675 680 685

Ser Val Pro Ala Gly Pro Pro Ala Gln Tyr Ser Val Thr Leu His Gly
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Gln Asp Val Leu Met Leu Pro Gly Asp Leu Val Gly Leu Gln His Asp
705 710 715 720

Ala Gly Pro Gly Ala Leu Leu His Cys Ser Pro Ala Pro Gly His Pro
725 730 735

Gly Pro Arg Ala Pro Tyr Leu Ser Ala Asn Ala Ser Ser Trp Leu Pro
740 745 750

His Leu Pro Ala Gln Leu Glu Gly Thr Trp Gly Cys Pro Ala Cys Ala
755 760 765

Leu Arg Leu Leu Ala Gln Arg Glu Gln Leu Thr Val Leu Leu Gly Leu
770 775 780

Arg Pro Asn Pro Gly Leu Arg Leu Pro Gly Arg Tyr Glu Val Arg Ala
785 790 795 800

Glu Val Gly Asn Gly Val Ser Arg His Asn Leu Ser Cys Ser Phe Asp
805 810 815

Val Val Ser Pro Val Ala Gly Leu Arg Val Ile Tyr Pro Ala Pro Arg
820 825 830

Asp Gly Arg Leu Tyr Val Pro Thr Asn Gly Ser Ala Leu Val Leu Gln
835 840 845

Val Asp Ser Gly Ala Asn Ala Thr Ala Thr Ala Arg Trp Pro Gly Gly
850 855 860

Ser Leu Ser Ala Arg Phe Glu Asn Val Cys Pro Ala Leu Val Ala Thr
865 870 875 880

Phe Val Pro Ala Cys Pro Trp Glu Thr Asn Asp Thr Leu Phe Ser Val
885 890 895

Val Ala Leu Pro Trp Leu Ser Glu Gly Glu His Val Val Asp Val Val
900 905 910

Val Glu Asn Ser Ala Ser Arg Ala Asn Leu Ser Leu Arg Val Thr Ala
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Glu Glu Pro Ile Cys Gly Leu Arg Ala Thr Pro Ser Pro Glu Ala Arg
930 935 940

Val Leu Gln Gly Val Leu Val Arg Tyr Ser Pro Val Val Glu Ala Gly
945 950 955 960

Ser Asp Met Val Phe Arg Trp Thr Ile Asn Asp Lys Gln Ser Leu Thr
965 970 975

Phe Gln Asn Val Val Phe Asn Val Ile Tyr Gln Ser Ala Ala Val Phe
980 985 990

Lys Leu Ser Leu Thr Ala Ser Asn His Val Ser Asn Val Thr Val Asn
995 1000 1005

Tyr Asn Val Thr Val Glu Arg Met Asn Arg Met Gln Gly Leu Gln Val
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Ser Thr Val Pro Ala Val Leu Ser Pro Asn Ala Thr Leu Ala Leu Thr
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Ala Gly Val Leu Val Asp Ser Ala Val Glu Val Ala Phe Leu Trp Thr
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Phe Gly Asp Gly Glu Gln Ala Leu His Gln Phe Gln Pro Pro Tyr Asn
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Glu Ser Phe Pro Val Pro Asp Pro Ser Val Ala Gln Val Leu Val Glu
1075 1080 1085

His Asn Val Thr His Thr Tyr Ala Ala Pro Gly Glu Tyr Leu Leu Thr
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Val Leu Ala Ser Asn Ala Phe Glu Asn Leu Thr Gln Gln Val Pro Val
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Ser Val Arg Ala Ser Leu Pro Ser Val Ala Val Gly Val Ser Asp Gly
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Val Leu Val Ala Gly Arg Pro Val Thr Phe Tyr Pro His Pro Leu Pro
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Ser Pro Gly Gly Val Leu Tyr Thr Trp Asp Phe Gly Asp Gly Ser Pro
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Val Leu Thr Gln Ser Gln Pro Ala Ala Asn His Thr Tyr Ala Ser Arg
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Gly Thr Tyr His Val Arg Leu Glu Val Asn Asn Thr Val Ser Gly Ala
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Asp Gly Thr Val Leu Ser Gly Pro Glu Ala Thr Val Glu His Val Tyr
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Leu Arg Ala Gln Asn Cys Thr Val Thr Val Gly Ala Gly Ser Pro Ala
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Gly His Leu Ala Arg Ser Leu His Val Leu Val Phe Val Leu Glu Val
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Leu Arg Val Glu Pro Ala Ala Cys Ile Pro Thr Gln Pro Asp Ala Arg
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Leu Thr Ala Tyr Val Thr Gly Asn Pro Ala His Tyr Leu Phe Asp Trp
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Thr Phe Gly Asp Gly Ser Ser Asn Thr Thr Val Arg Gly Cys Pro Thr
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Val Thr His Asn Phe Thr Arg Ser Gly Thr Phe Pro Leu Ala Leu Val
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Leu Ser Ser Arg Val Asn Arg Ala His Tyr Phe Thr Ser Ile Cys Val
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Glu Pro Glu Val Gly Asn Val Thr Leu Gln Pro Glu Arg Gln Phe Val
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Gln Leu Gly Asp Glu Ala Trp Leu Val Ala Cys Ala Trp Pro Pro Phe
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Pro Tyr Arg Tyr Thr Trp Asp Phe Gly Thr Glu Glu Ala Ala Pro Thr
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Arg Ala Arg Gly Pro Glu Val Thr Phe Ile Tyr Arg Asp Pro Gly Ser
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Tyr Leu Val Thr Val Thr Ala Ser Asn Asn Ile Ser Ala Ala Asn Asp
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Ser Ala Leu Val Glu Val Gln Glu Pro Val Leu Val Thr Ser Ile Lys
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Val Asn Gly Ser Leu Gly Leu Glu Leu Gln Gln Pro Tyr Leu Phe Ser
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Lys Gly Phe Ser Leu Thr Val Leu Glu Ala Gly Thr Tyr His Val Gln
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Thr Val Glu Val Asp Val Gln Val Pro Val Ser Gly Leu Ser Ile Arg
1795 1800 1805

Ala Ser Glu Pro Gly Gly Ser Phe Val Ala Ala Gly Ser Ser Val Pro
1810 1815 1820

Phe Trp Gly Gln Leu Ala Thr Gly Thr Asn Val Ser Trp Cys Trp Ala
825 1830 1835 1840

Val Pro Gly Gly Ser Ser Lys Arg Gly Pro His Val Thr Met Val Phe
1845 1850 1855

Pro Asp Ala Gly Thr Phe Ser Ile Arg Leu Asn Ala Ser Asn Ala Val
1860 1865 1870

Ser Trp Val Ser Ala Thr Tyr Asn Leu Thr Ala Glu Glu Pro Ile Val
1875 1880 1885

Gly Leu Val Leu Trp Ala Ser Ser Lys Val Val Ala Pro Gly Gln Leu
1890 1895 1900

Val His Phe Gln Ile Leu Leu Ala Ala Gly Ser Ala Val Thr Phe Arg
1905 1910 1915 1920

Leu Gln Val Gly Gly Ala Asn Pro Glu Val Leu Pro Gly Pro Arg Phe
1925 1930 1935

Ser His Ser Phe Pro Arg Val Gly Asp His Val Val Ser Val Arg Gly
1940 1945 1950

Lys Asn His Val Ser Trp Ala Gln Ala Gln Val Arg Ile Val Val Leu
1955 1960 1965

Glu Ala Val Ser Gly Leu Gln Val Pro Asn Cys Cys Glu Pro Gly Ile
1970 1975 1980

Ala Thr Gly Thr Glu Arg Asn Phe Thr Ala Arg Val Gln Arg Gly Ser
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Arg Val Ala Tyr Ala Trp Tyr Phe Ser Leu Gln Lys Val Gln Gly Asp
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Ser Leu Val Ile Leu Ser Gly Arg Asp Val Thr Tyr Thr Pro Val Ala
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Lys Ser Asn Phe Phe Val Leu Leu Leu Leu Ala Ile Ser Ala Ile Gln
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Leu Asp Asn Asp Asp Thr Thr Ile Gly Gly Val Pro Arg Asn Ser Gln
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Gly Val Val Lys Ile Lys Leu Ser Cys Gly Leu Asn Arg Leu Ser Val
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Glu Asn Lys Val Thr Glu Val Ser Ser Leu Glu Leu Ile His Asn Cys
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Gly Ser Leu Trp Trp Leu Gln Val Gly Gly Asn Glu Met Ala Leu Leu
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930 935 940

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Arg Thr Thr Thr Val Asp Pro Asp Ala Ser Thr Glu Thr Pro Tyr Asp

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1845 1850 1855

Ser Pro Ala Ser Thr Leu Asn Thr Ala Glu Ile Thr Asp Lys Thr Leu
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Asp Asn Phe Asp Met Leu Ile Thr Ser Gly Ala Leu Glu Ala His Ile
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Glu Thr Phe Leu Arg Asn Pro Tyr Gly Lys Ile Glu Lys Gly Leu Gly
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Thr Glu Ile Ala Asp Val Thr Lys Leu Arg Asp Thr Glu Asn Arg Lys
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Met Arg Asp Glu Gln Leu Phe Ile Thr Ile Arg Asp Met Leu Cys Phe
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Phe Ala Ser Leu Tyr Ile Met Val Met Leu Thr Tyr Tyr Cys Lys Asp
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Arg His Gly Tyr Trp Tyr Gln Leu Glu Met Ser Thr Ile Leu Asn Ile
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Ala Ser Trp Tyr Asp Gly Asn Pro Ala Tyr Gly Met Arg Ala Tyr Met
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Asn Asp Lys Val Ser Arg Ser Met Gly Ile Gly Thr Ile Arg Gln Val
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Arg Thr Lys Lys Ser Ala Glu Cys Thr Met Phe Lys Gln Phe Gln Gly
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Tyr Ile Asn Asp Cys Gly Glu Glu Leu Thr Ser Lys Asn Glu Glu Lys
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Pro Gln Pro Val Ala Ala Ala Glu His Gly Pro Ser Phe Asp His Ser
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<220>
<223> Description of Artificial Sequence: Outside primer for PCR screening of *lov-1* genomic (*sy582*) deletion

<400> 7
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<210> 8
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Outside primer for PCR screening of *lov-1* genomic (*sy582*) deletion

<400> 8
gggagtttcc gttttcatgg gg 22

<210> 9
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Nested primer for PCR screening of *lov-1* genomic (*sy582*) deletion

<400> 9
ctaggaccga tgcaacagcg ag 22

<210> 10
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Nested primer for PCR screening of *lov-1* genomic (*sy582*) deletion

<400> 10
aacgctgatt ggttcaagtg tg 22

<210> 11
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Outside primer for PCR screening of *pkd-2* genomic (*sy606*) deletion

<400> 11
cccctcgttt gaccattcta tgg 23

<210> 12
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Outside primer for PCR screening of *pkd-2* genomic (*sy606*) deletion

<400> 12
acgtgatcct ctgtcgatcc ag 22

<210> 13
<211> 22

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Nested primer for PCR screening of *pkd-2* genomic (*sy606*) deletion

<400> 13
agatcaagct gactgcccgt tc 22

<210> 14
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Nested primer for PCR screening of *pkd-2* genomic (*sy606*) deletion

<400> 14
gatccagcga ttagccttta acg 23

<210> 15

<211> 2870
<212> PRT
<213> C. Elegans Lov-1 *sy582* deletion protein

<400> 15

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 1               5                  10                  15

Phe Ser Cys Cys Leu Phe Cys Ser Glu Phe Ile Phe Val Phe Arg Arg
            20                  25                  30

Ile Phe Thr Lys Leu Leu Gln Asp Asn Leu Pro Ala His Trp Met Lys
        35                  40                  45

Lys Ser Asn Phe Phe Val Leu Leu Leu Leu Ala Ile Ser Ala Ile Gln
    50                  55                  60

Ile Asp Gly Leu His Tyr Gln Leu Leu Asp Gly Ile Ala Thr Phe Arg
65                  70                  75                  80

Leu Asp Asn Asp Asp Thr Thr Ile Gly Gly Val Pro Arg Asn Ser Gln
                85                  90                  95

Gly Val Val Lys Ile Lys Leu Ser Cys Gly Leu Asn Arg Leu Ser Val
            100                 105                 110

Glu Asn Lys Val Thr Glu Val Ser Ser Leu Glu Leu Ile His Asn Cys
        115                 120                 125

Ile Gln Thr Glu Thr Arg Leu Val Gly Leu Phe Leu Asn Ser Thr Trp
    130                 135                 140

Ile Thr Leu Asn Glu Val Asn Asp Asp Asp Glu Ile Ser Ile Ala Val
145                 150                 155                 160

Glu Ala Lys Tyr Glu Val Cys Tyr Asp Asp Gly Ile Asp Arg Cys Asp
                165                 170                 175

Gly Ser Leu Trp Trp Leu Gln Val Gly Gly Asn Glu Met Ala Leu Leu
            180                 185                 190

Gly Tyr Arg Glu Lys Cys Glu Ser Gly Glu Ile Asn Glu Glu Tyr Ala
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195 200 205

Arg Arg Met Cys Lys Arg Pro Tyr Arg Ser Glu Lys Ser Thr Ala Ile
210 215 220

Ser Asp Ser Gln Gly Val Tyr Tyr Asp Gly Gln Val Leu Lys Gly Val
225 230 235 240

Arg Ala Lys Gln Phe Ser Met Arg Thr Ser Gly Ser Pro Thr Leu Arg
245 250 255

Arg Met Lys Arg Asp Ala Gly Asp Asn Thr Cys Asp Tyr Thr Ile Glu
260 265 270

Ser Thr Ser Thr Ser Thr Thr Thr Pro Thr Thr Thr Thr Val Thr Ser
275 280 285

Thr Val Thr Ser Thr Thr Thr Val Pro Thr Ser Thr Ser Thr Val Thr
290 295 300

Thr Ala Met Ser Thr Ser Thr Ser Thr Pro Ser Thr Ser Thr Thr Ile
305 310 315 320

Glu Ser Thr Ser Thr Thr Phe Thr Ser Thr Ala Ser Thr Ser Thr Ser
325 330 335

Ser Thr Ser Thr Thr Gln Gln Ser Ser Ser Thr Ile Thr Ser Ser Pro
340 345 350

Ser Ser Thr Thr Leu Ser Thr Ser Ile Pro Thr Thr Thr Thr Pro Glu
355 360 365

Ile Thr Ser Thr Leu Ser Ser Leu Pro Asp Asn Ala Ile Cys Ser Tyr
370 375 380

Leu Asp Glu Thr Thr Thr Ser Thr Thr Phe Thr Thr Thr Met Leu Thr
385 390 395 400

Ser Thr Thr Thr Glu Glu Pro Ser Thr Ser Thr Thr Thr Thr Glu Val
405 410 415

Thr Ser Thr Ser Ser Thr Val Thr Thr Thr Glu Pro Thr Thr Thr Leu
420 425 430

Thr Thr Ser Thr Ala Ser Thr Ser Thr Thr Glu Pro Ser Thr Ser Thr
435 440 445

Val Thr Thr Ser Pro Ser Thr Ser Pro Val Thr Ser Thr Val Thr Ser
450 455 460

Ser Ser Ser Ser Ser Thr Thr Val Thr Thr Pro Thr Ser Thr Glu Ser
465 470 475 480

Thr Ser Thr Ser Pro Ser Ser Thr Val Thr Thr Ser Thr Thr Ala Pro
485 490 495

Ser Thr Ser Thr Thr Gly Pro Ser Ser Ser Ser Ser Thr Pro Ser Ser
500 505 510

Thr Ala Ser Ser Ser Val Ser Ser Thr Ala Ser Ser Thr Gln Ser Ser
515 520 525

Thr Ser Thr Gln Gln Ser Ser Thr Thr Thr Lys Ser Glu Thr Thr Thr
530 535 540

Ser Ser Asp Gly Thr Asn Pro Asp Phe Tyr Phe Val Glu Lys Ala Thr

545 550 555 560

Thr Thr Phe Tyr Asp Ser Thr Ser Val Asn Leu Thr Leu Asn Ser Gly
565 570 575

Leu Gly Ile Ile Gly Tyr Gln Thr Ser Ile Glu Cys Thr Ser Pro Thr
580 585 590

Ser Ser Asn Tyr Val Ser Thr Thr Lys Asp Gly Ala Cys Phe Thr Lys
595 600 605

Ser Val Ser Met Pro Arg Leu Gly Gly Thr Tyr Pro Ala Ser Thr Phe
610 615 620

Val Gly Pro Gly Asn Tyr Thr Phe Arg Ala Thr Met Thr Thr Asp Asp
625 630 635 640

Lys Lys Val Tyr Tyr Thr Tyr Ala Asn Val Tyr Ile Gln Glu Tyr Ser
645 650 655

Ser Thr Thr Ile Glu Ser Glu Ser Ser Thr Ser Ala Val Ala Ser Ser
660 665 670

Thr Ser Ser Thr Pro Ser Thr Pro Ser Ser Thr Leu Ser Thr Ser Thr
675 680 685

Val Thr Glu Pro Ser Ser Thr Arg Ser Ser Asp Ser Thr Thr Thr Ser
690 695 700

Ala Gly Ser Thr Thr Thr Leu Gln Glu Ser Thr Thr Thr Ser Glu Glu
705 710 715 720

Ser Thr Thr Asp Ser Ser Thr Thr Thr Ile Ser Asp Thr Ser Thr Ser
725 730 735

Thr Ser Ser Pro Ser Ser Thr Thr Ala Asp Ser Thr Ser Thr Leu Ser
740 745 750

Val Asp Gln Phe Asp Phe Ile Leu Asp Ser Gly Leu Ser Trp Asn Glu
755 760 765

Thr Arg His Asn Glu Asp Ser Ile Asn Ile Val Pro Leu Pro Thr Asn
770 775 780

Ala Ile Thr Pro Thr Glu Arg Ser Gln Thr Phe Glu Cys Arg Asn Val
785 790 795 800

Ser Thr Glu Pro Phe Leu Ile Ile Lys Glu Ser Thr Cys Leu Asn Tyr
805 810 815

Ser Asn Thr Val Leu Asn Ala Thr Tyr Ser Ser Asn Ile Pro Ile Gln
820 825 830

Pro Ile Glu Thr Phe Leu Val Gly Ile Gly Thr Tyr Glu Phe Arg Ile
835 840 845

Asn Met Thr Asp Leu Thr Thr Met Gln Val Val Ser His Ile Phe Thr
850 855 860

Leu Asn Val Val Ala Asp Ser Thr Ser Thr Ser Glu Val Thr Ser Thr
865 870 875 880

Thr Ser Thr Gly Ser Ser Ser Glu Ser Ser Ala Ile Ser Thr Thr Ser
885 890 895

Gly Ile Glu Ser Thr Ser Thr Leu Glu Ala Ser Thr Thr Asp Ala Ser

900 905 910

Gln Asp Ser Ser Thr Ser Thr Ser Asp Ser Gly Thr Thr Ser Asp Ser
915 920 925

Thr Thr Ile Asp Ser Ser Asn Ser Thr Pro Ser Thr Ser Asp Ser Ser
930 935 940

Gly Leu Ser Gln Thr Pro Ser Asp Ser Ser Ser Ala Ser Asp Ser Met
945 950 955 960

Arg Thr Thr Thr Val Asp Pro Asp Ala Ser Thr Glu Thr Pro Tyr Asp
965 970 975

Phe Val Leu Glu Asn Leu Thr Trp Asn Glu Thr Val Tyr Tyr Ser Glu
980 985 990

Asn Pro Phe Tyr Ile Thr Pro Ile Pro Asn Lys Glu Pro Gly Ala Leu
995 1000 1005

Thr Thr Ala Met Thr Cys Gln Cys Arg Asn Asp Ser Ser Gln Pro Phe
1010 1015 1020

Val Leu Leu Lys Glu Ser Asn Cys Leu Thr Glu Phe Gly Lys Asn Gly
1025 1030 1035 1040

Ala Tyr Ser Ala Ser Val Ser Phe Asn Pro Met Thr Ser Phe Val Pro
1045 1050 1055

Ala Thr Gly Thr Tyr Glu Phe Leu Ile Asn Val Thr Asn Arg Ala Ser
1060 1065 1070

Gly Glu Ser Ala Ser His Ile Phe Thr Met Asn Val Val Leu Pro Thr
1075 1080 1085

Thr Thr Thr Glu Thr Pro Pro Thr Thr Val Ser Ser Ser Asp Asp Ala
1090 1095 1100

Gly Gly Lys Thr Gly Gly Thr Gly Ala Thr Gly Gly Thr Gly Gly Thr
1105 1110 1115 1120

Gly Ser Gly Gly Ser Ala Thr Thr Leu Ser Thr Gly Asp Ala Val Arg
1125 1130 1135

Ser Thr Thr Ser Gly Ser Gly Ser Gly Gln Ser Ser Thr Gly Ser Gly
1140 1145 1150

Ala Gly Gly Ser Gly Thr Thr Ala Ser Gly Ser Gly Ser Gly Gly Ser
1155 1160 1165

Ser Gly Thr Gly Ser Asp Gly Val Asn Ser Gly Lys Thr Thr Ala Leu
1170 1175 1180

Asn Gly Asp Gly Thr Gly Ser Gly Thr Ala Thr Thr Pro Gly Ser His
1185 1190 1195 1200

Leu Gly Asp Gly Gly Ser Thr Ser Gly Ser Gly Ser Asp Ser Asn Gly
1205 1210 1215

Ser Ser Gly Val Ser Thr Lys Ser Ser Ser Gly Ser Asp Thr Ser Gly
1220 1225 1230

Ser Ser Asp Ser Ser Gly Ala Asn Gly Ala Phe Ser Ala Thr Ala Gln
1235 1240 1245

Pro Ser Thr Arg Thr Thr Lys Thr Arg Ser Ser Leu Ala Thr Val Ser
1250 1255 1260

Pro Ile Ser Ala Ala Glu Gln Ala Ile Ile Asp Ala Gln Lys Ala Asp
1265 1270 1275 1280

Val Met Asn Gln Leu Ala Gly Ile Met Asp Gly Ser Ala Ser Asn Asn
1285 1290 1295

Ser Leu Asn Thr Ser Ser Ser Leu Leu Asn Gln Ile Ser Ser Leu Pro
1300 1305 1310

Ala Ala Asp Leu Val Glu Val Ala Gln Ser Leu Leu Ser Asn Thr Leu
1315 1320 1325

Lys Ile Pro Gly Val Gly Asn Met Ser Ser Val Asp Val Leu Lys Thr
1330 1335 1340

Leu Gln Asp Asn Ile Ala Thr Thr Asn Ser Glu Leu Ala Asp Glu Met
1345 1350 1355 1360

Ala Lys Val Ile Thr Lys Leu Ala Asn Val Asn Met Thr Ser Ala Gln
1365 1370 1375

Ser Leu Asn Ser Val Leu Ser Ser Leu Asp Leu Ala Leu Lys Gly Ser
1380 1385 1390

Thr Val Tyr Thr Leu Gly Val Ser Ser Thr Lys Ser Lys Asp Gly Thr
1395 1400 1405

Tyr Ala Val Ile Phe Gly Tyr Val Ile Ala Ser Gly Tyr Thr Leu Val
1410 1415 1420

Ser Pro Arg Cys Thr Leu Ser Ile Tyr Gly Ser Thr Ile Tyr Leu Thr
1425 1430 1435 1440

Gly Asp Thr Arg Ala Ser Tyr Lys Gln Leu Asp Gly Asp Thr Val Thr
1445 1450 1455

Ala Asp Thr Met Leu Ala Ala Ala Ile Gly Ile Gln Gly Met Phe Ala
1460 1465 1470

Thr Asn Gly Arg Thr Val Gln Val Glu Gln Asp Lys Ile Asp Asp Lys
1475 1480 1485

Arg Ser Leu Val Ser Gly Asn Ile Met Ala Thr Met Ser Gly Val Gly
1490 1495 1500

Asp Val Gln Ser Gly Glu Tyr Ser Tyr Asn Asp Met Tyr Val Thr Ala
1505 1510 1515 1520

Trp Asn Val Thr Tyr Asp Asn Ser Thr Val Gly Ser Thr Ser Gln Lys
1525 1530 1535

Asn Thr Ser Phe Ser Phe Asn Ile Pro Val Ser Glu Val Gln Tyr Ile
1540 1545 1550

Leu Leu Ile Glu Ser Gly Thr Met Ile Lys Leu His Ser Thr Gln Asn
1555 1560 1565

Ile Val Ser Arg Gly Leu Val Val Thr Ala Ser Tyr Gly Gly Val Thr
1570 1575 1580

Tyr Thr Ile Thr Cys Thr Asn Gly Thr Gly Lys Phe Val Glu Val Asp
1585 1590 1595 1600

Thr Asp Asn Ala Ile Phe Ser Tyr Asn Ala Asp Ser Phe Thr Val Val
1605 1610 1615

Ala Ser Asp Gly Ser Ser Ala Ser Thr Val Lys Lys Leu Ile Gln Met
1620 1625 1630

Pro Ile Val Ile Glu Asn Val Asn Leu Ala Leu Phe Asn Gln Thr Thr
1635 1640 1645

Ser Pro Leu Val Phe Ser Asn Ala Gly Ser Tyr Ser Met Arg Met Val
1650 1655 1660

Leu Ser Pro Gln Asp Ile Gly Ile Pro Ala Val Ser Ala Leu Ser Gln
1665 1670 1675 1680

Thr Val Ser Ile Ser Thr Leu Ser Pro Thr Ala Ser Tyr Thr Lys Asp
1685 1690 1695

Asp Leu Gln Ser Leu Ile Lys Glu Gln Thr Leu Val Thr Val Ser Gly
1700 1705 1710

Thr Thr Ser Asn Ser Leu Leu Ser Ile Ala Gly Ser Leu Thr Ser Ala
1715 1720 1725

Leu Lys Ile Ala Leu Asp Asn Pro Leu Ser Ser Asp Leu Ala Ala Asn
1730 1735 1740

Leu Lys Tyr Ala Thr Asp Asn Tyr Asp Ser Leu Tyr Asn Val Leu Pro
1745 1750 1755 1760

Ser Asp Pro Asp Asn Ile Val Tyr Val Glu Glu Met Thr Ser Glu Glu
1765 1770 1775

Trp Ala Ala Tyr Val Thr Lys Met Phe Gln Lys Asn Ile Ala Lys Asn
1780 1785 1790

Leu Ala Asn Gln Leu Ala Ser Thr Leu Asp Thr Leu Glu Asn Thr Leu
1795 1800 1805

Ala Ala Arg Ala Ile Ala Thr Gly Asn Leu Pro Tyr Asp Tyr Ser Asn
1810 1815 1820

Ser Val Asp Gly Thr Gly Met Val Ile Val Ile Asp Asp Ala Ser Asn
1825 1830 1835 1840

Ile Val Gly Lys Thr Gln Asn Cys Glu Glu Trp Ala Phe Lys Leu Pro
1845 1850 1855

Ser Pro Ala Ser Thr Leu Asn Thr Ala Glu Ile Thr Asp Lys Thr Leu
1860 1865 1870

Ile Gln Val Gly Leu Val Cys Tyr Ala Thr Asn Pro Arg Thr Tyr Val
1875 1880 1885

Asp Asn Phe Asp Met Leu Ile Thr Ser Gly Ala Leu Glu Ala His Ile
1890 1895 1900

Lys Asp Glu Asn Gln Ile Ile Ile Pro Ile Thr Gly Thr Thr Ala Pro
1905 1910 1915 1920

Ile Tyr Val Asn Gly Arg Gly Ser Glu Asp Asp Ala Val Leu Thr Leu
1925 1930 1935

Met Gln Gln Gly Asp Phe Ala Ser Tyr Gln Ile Leu Asp Leu His Ala
1940 1945 1950

Phe Arg Thr Thr Asn Trp Asn Asn Ser Leu Gln Val Glu Ile Ile Ala
1955 1960 1965

Ser Gln Asp Tyr Glu Ile Pro Asn Asn Asp Asp Thr Tyr Met Phe Ser

1970 1975 1980

Ser Phe Gln Ser Leu Pro Gly Pro Leu Glu Ser Asn His Glu Trp Ile
1985 1990 1995 2000

Phe Asp Leu Asn Thr Leu Asn Lys Thr Ser Asn Tyr Phe Val Thr Ala
2005 2010 2015

Gly Asn Leu Ile Asn Asn Thr Gly Leu Phe Phe Ile Gly Ile Gly Lys
2020 2025 2030

Arg Asn Ser Ser Thr Asn Thr Gly Asn Ser Ser Asp Ile Val Asn Tyr
2035 2040 2045

Gly Gln Tyr Asp Ser Met Gln Trp Ser Phe Ala Arg Ser Val Pro Met
2050 2055 2060

Asp Tyr Gln Val Ala Ala Val Ser Lys Gly Cys Tyr Phe Tyr Gln Lys
2065 2070 2075 2080

Thr Ser Asp Val Phe Asn Ser Glu Gly Met Tyr Pro Ser Asp Gly Gln
2085 2090 2095

Gly Met Gln Phe Val Asn Cys Ser Thr Asp His Leu Thr Met Phe Ser
2100 2105 2110

Val Gly Ala Phe Asn Pro Thr Ile Asp Ala Asp Phe Ser Tyr Asn Tyr
2115 2120 2125

Asn Val Asn Glu Ile Glu Lys Asn Val Lys Val Met Ile Ala Ala Val
2130 2135 2140

Phe Met Leu Val Val Tyr Gly Cys Leu Thr Ile Asn Ala Ile Ile Cys
2145 2150 2155 2160

Gln Arg Lys Asp Ala Ser Arg Gly Arg Leu Arg Phe Leu Lys Asp Asn
2165 2170 2175

Glu Pro His Asp Gly Tyr Met Tyr Val Ile Ala Val Glu Thr Gly Tyr
2180 2185 2190

Arg Met Phe Ala Thr Thr Asp Ser Thr Ile Cys Phe Asn Leu Ser Gly
2195 2200 2205

Asn Glu Gly Asp Gln Ile Phe Arg Ser Phe Arg Ser Glu Glu Asp Gly
2210 2215 2220

Asn Trp Glu Phe Pro Phe Ser Trp Gly Thr Thr Asp Arg Phe Val Met
2225 2230 2235 2240

Thr Thr Ala Phe Pro Leu Gly Glu Leu Glu Tyr Met Arg Leu Trp Leu
2245 2250 2255

Asp Asp Ala Gly Leu Asp His Arg Glu Ser Trp Tyr Cys Asn Arg Ile
2260 2265 2270

Ile Val Lys Asp Leu Gln Thr Gln Asp Ile Tyr Tyr Phe Pro Phe Asn
2275 2280 2285

Asn Trp Leu Gly Thr Lys Asn Gly Asp Gly Glu Thr Glu Arg Leu Ala
2290 2295 2300

Arg Val Glu Tyr Lys Arg Arg Phe Leu Asp Glu Ser Met Ser Met His
2305 2310 2315 2320

Met Leu Ala Gln Thr Ile Ser Trp Phe Ala Met Phe Thr Gly Gly Gly

2325 2330 2335

Asn Arg Leu Arg Asp Arg Val Ser Arg Gln Asp Tyr Ser Val Ser Ile
2340 2345 2350

Ile Phe Ser Leu Val Val Val Ser Met Ile Ser Ile Thr Ile Leu Lys
2355 2360 2365

Ser Asp Asn Ser Ile Ile Ser Asp Ser Lys Ser Val Ser Glu Phe Thr
2370 2375 2380

Phe Thr Ile Lys Asp Ile Ala Phe Gly Val Gly Phe Gly Val Leu Ile
2385 2390 2395 2400

Thr Phe Leu Asn Ser Leu His Ile Leu Leu Cys Thr Lys Cys Arg Ser
2405 2410 2415

His Ser Glu His Tyr Tyr Tyr Lys Lys Arg Lys Arg Glu Asp Pro Glu
2420 2425 2430

Phe Lys Asp Asn Ser Gly Ser Trp Pro Met Phe Met Ala Gly Met Ala
2435 2440 2445

Arg Thr Ile Ile Val Phe Pro Val Leu Met Gly Leu Ile Tyr Ile Ser
2450 2455 2460

Gly Ala Gly Met Ser Leu Met Asp Asp Leu Ala Asn Ser Phe Tyr Ile
2465 2470 2475 2480

Arg Phe Leu Ile Ser Leu Ile Leu Trp Ala Val Val Phe Glu Pro Ile
2485 2490 2495

Lys Gly Leu Ile Trp Ala Phe Leu Ile Leu Lys Thr Arg Lys Ser His
2500 2505 2510

Lys Ile Ile Asn Lys Leu Glu Gly Ser Asp Gly Thr Val Val Lys Tyr
2515 2520 2525

Tyr Glu Met Leu Tyr Ile Phe Phe Ser Val Leu Ile Phe Val Lys Glu
2530 2535 2540

Ile Val Phe Tyr Leu Tyr Gly Arg Tyr Lys Val Ile Thr Thr Met Lys
2545 2550 2555 2560

Pro Thr Arg Asn Pro Phe Lys Ile Val Tyr Gln Leu Ala Leu Gly Asn
2565 2570 2575

Phe Ser Pro Trp Asn Phe Met Asp Leu Ile Val Gly Ala Leu Ala Val
2580 2585 2590

Ala Ser Val Leu Ala Tyr Thr Ile Arg Gln Arg Thr Thr Asn Arg Ala
2595 2600 2605

Met Glu Asp Phe Asn Ala Asn Asn Gly Asn Ser Tyr Ile Asn Leu Thr
2610 2615 2620

Glu Gln Arg Asn Trp Glu Ile Val Phe Ser Tyr Cys Leu Ala Gly Ala
2625 2630 2635 2640

Val Phe Phe Thr Ser Cys Lys Met Ile Arg Ile Leu Arg Phe Asn Arg
2645 2650 2655

Arg Ile Gly Val Leu Ala Ala Thr Leu Asp Asn Ala Leu Gly Ala Ile
2660 2665 2670

Val Ser Phe Gly Ile Ala Phe Leu Phe Phe Ser Met Thr Phe Asn Ser

2675 2680 2685

Val Leu Tyr Ala Val Leu Gly Asn Lys Met Gly Gly Tyr Arg Ser Leu
2690 2695 2700

Met Ala Thr Phe Gln Thr Ala Leu Ala Gly Met Leu Gly Lys Leu Asp
2705 2710 2715 2720

Val Thr Ser Ile Gln Pro Ile Ser Gln Phe Ala Phe Val Val Ile Met
2725 2730 2735

Leu Tyr Met Ile Ala Gly Ser Lys Leu Val Leu Gln Leu Tyr Val Thr
2740 2745 2750

Ile Ile Met Phe Glu Phe Glu Glu Ile Arg Asn Asp Ser Glu Lys Gln
2755 2760 2765

Thr Asn Asp Tyr Glu Ile Ile Asp His Ile Lys Tyr Lys Thr Lys Arg
2770 2775 2780

Arg Leu Gly Leu Leu Glu Pro Lys Asp Phe Ala Pro Val Ser Ile Ala
2785 2790 2795 2800

Asp Thr Gln Lys Asp Phe Arg Leu Phe His Ser Ala Val Ala Lys Val
2805 2810 2815

Asn Leu Leu His His Arg Ala Thr Arg Met Leu Gln Thr Gln Gly Gln
2820 2825 2830

Tyr Gln Asn Gln Thr Val Ile Asn Tyr Thr Leu Ser Tyr Asp Pro Val
2835 2840 2845

Ser Ala Ile His Glu Thr Gly Pro Lys Arg Phe Gln Lys Trp Arg Leu
2850 2855 2860

Asn Asp Val Glu Lys Asp
2865 2870

<210> 16
<211> 200
<212> PRT
<213> C. Elegans Pkd-2 deletion mutant (*sy606*) protein

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Met Glu Gly Arg Gly Glu Gly Glu Asp Leu Pro Pro Thr Ser Tyr Phe
1 5 10 15

Pro Phe Glu Glu Gly His Thr Leu Trp Met Lys Arg Glu Lys Ile Lys
20 25 30

His Leu Gln Arg Ile Leu Gln Phe His Ser Asp Glu Ser Ile Leu Met
35 40 45

Ile Asp Lys Lys Leu Met Ile Ser Gly Gly Leu Glu Pro Pro Thr Phe
50 55 60

Cys Val Leu Asp Arg Cys Asp Asn His Tyr Thr Thr Lys Pro Arg His
65 70 75 80

Leu Pro Pro Phe Glu Val Phe Leu Phe Val Val Ile Phe Lys Cys Glu
85 90 95

Pro Ser Ser Met Asn Tyr Gly Ala Ala Asp Glu Arg Trp Ala Asn Pro
100 105 110

Pro Gln Pro Val Ala Ala Ala Glu His Gly Pro Ser Phe Asp His Ser
115 120 125

Met Val Ser Glu Glu Tyr Glu His Asp Lys Lys Lys Asn Pro Ala Gln
130 135 140

Lys Glu Gly Ile Ser Phe Ser Gln Ala Leu Leu Ala Ser Gly His Glu
145 150 155 160

Lys Ser Asp Gly Lys Ile Lys Leu Thr Ala Arg Ser Phe Met Glu Val
165 170 175

Gly Gly Tyr Ala Val Phe Leu Ile Val Leu Val Tyr Asp Ser Ser Thr
180 185 190

Pro Arg Gln Lys Ser Leu Lys Thr
195 200